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Archives of Internal Medicine

VOLUME 53 APRIL, 1934 NUMBER 4

INFECTIONS WITH PNEUMOCOCCUS TYPE III AND TYPE VIII

CHARACTERIZATION OF PNEUMONIA CAUSED BY PNEUMOCOCCUS TYPE III AND THAT ASSOCIATED WITH A BIOLOGICALLY CLOSELY RELATED ORGANISM, PNEUMOCOCCUS TYPE VIII

MAXWELL FINLAND, M.D.
BOSTON
AND
W. D. SUTLIFF, M.D.
CHICAGO

The classification of pneumococci into serologically specific types [1] has rendered possible a thorough study of the distribution of these organisms in health and in disease. The investigation had its inception in relation to lobar pneumonia, but it soon became apparent that this clinical entity comprises a group of specific infectious diseases, alike in their clinical and anatomic manifestations but differing etiologically.[2] The significance of this distinction between the etiologic, as contrasted with the clinico-anatomic, classification has become increasingly important with the advent of serum therapy, which thus far has been shown to be strictly type specific in its action.

Furthermore, this consciousness of the responsible bacterial incitant has indicated that the reverse is also true; that is, the same organism, belonging to the same serologic type, may give rise to different clinical pictures in different persons. The latter fact is not emphasized as frequently as the former, because most writers have been interested primarily in lobar pneumonia. When, however, the disease picture associated with each type of pneumococcus is studied, it becomes clear that the

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Read before the Section on Pathology and Physiology at the Eighty-Fourth Annual Session of the American Medical Association, Milwaukee, June 15, 1933.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

1. (*a*) Dochez, A. R., and Gillespie, L. J.: A Biological Classification of Pneumococci by Means of Immunity Reactions, J. A. M. A. **61**:727 (Sept. 6) 1913. (*b*) Cooper, G.; Rosenstein, C.; Walter, A., and Peizer, L.: The Further Separation of Types Among the Pneumococci Hitherto Included in Group IV and the Development of Therapeutic Antisera for Those Types, J. Exper. Med. **55**:531 (April) 1932.

2. Cole, R.: Acute Pulmonary Infections, De Lamar Lectures, 1927-1928, Baltimore, Williams & Wilkins Company, 1928.

different types vary in the uniformity with which they produce lobar pneumonia, "atypical" pneumonia or bronchopneumonia or focal infections without pneumonia. Epidemiologic investigations [3] and bacteriologic studies in a variety of cases without or with other pulmonary diseases have also indicated wide variations in the frequency with which the various types of pneumococci occur without demonstrable relation to disease.[4] Cole [2] and more recently Gundel [5] have emphasized the uniformity with which types I and II are associated with primary lobar pneumonia. Most of the other types are less uniform in the character of the disease that they produce.[4a] Types III and VIII, with which this paper is concerned, are notable examples of types which are not associated with a uniform clinico-anatomic disease.

The type III pneumococcus has a number of distinctive bacteriologic, immunologic and epidemiologic features. Because of its large capsule and its tendency to grow in chains and produce a large mucoid colony on the surface of enriched solid mediums, it has been known variously as "Streptococcus capsulatus," "Streptococcus mucosus" and "Pneumococcus mucosus." An organism of this description was early recognized in spontaneous diseases in animals.[6] In man, it was isolated first from a case of meningitis [7] and then from other inflammatory lesions.[8] Its

3. Stillman, E. G.: Further Studies on the Epidemiology of Lobar Pneumonia, J. Exper. Med. **26**:513 (Oct.) 1917. Rosenau, M. J.; Felton, L. D., and Atwater, R. M.: An Epidemiologic Study of Pneumonia and Its Mode of Spread, Am. J. Hyg. **6**:463 (May) 1926. Powell, J. P.; Atwater, R. M., and Felton, L. D.: The Epidemiology of Pneumonia, Am. J. Hyg. **6**:570 (July) 1926. Webster, L. T., and Hughes, T. P.: Incidence and Spread of Pneumococci in Nasal Passages and Throats of Healthy Persons, J. Exper. Med. **53**:535 (April) 1931. Gundel, M.: Bakteriologie und epidemiologische Untersuchungen über die Besiedlung der oberen Atmungswege Gesunder mit Pneumokokken, Ztschr. f. Hyg. u. Infektionskr. **114**:659, 1933. Smillie, W. G.: The Epidemiology of Lobar Pneumonia: A Study of the Prevalence of Specific Strains of Pneumococci in the Nasopharynx of Immediate Family Contacts, J. A. M. A. **101**:1281 (Oct. 31) 1933.

4. (*a*) Sutliff, W. D., and Finland, M.: The Significance of the Newly Classified Types of Pneumococci in Disease: Types IV to XX Inclusive, J. A. M. A. **101**:1289 (Oct. 31) 1933. (*b*) Cooper et al.[1b]

5. Gundel, M.: Die Bakteriologie, Epidemiologie, und spezifische Therapie der Pneumokokken-Infektionen des Menschen unter besonderer Berücksichtigung der Pneumonie, Ergebn. d. Hyg., Bakt., Immunitätsforsch. u. exper. Therap. **12**: 129, 1931.

6. Poels, J., and Nolen, W.: Das Contagium der Lungenseuche, Fortschr. d. Med. **4**:217, 1886. Benaghi, R.: Ueber einen Streptococcus capsulatus, Centralbl. f. Bakt. (Abt. 1) **22**:273, 1897.

7. Bonome, A.: Zur Aetiologie der Meningitis cerebro-spinalis epidemica, Beitr. z. path. Anat. u. z. allg. Path. **8**:377, 1890.

8. Atkinson, R. T.: A Pathogenic Diplococcus, J. Boston Soc. M. Sc. **1**:2, 1897. Howard, W. T., and Perkins, R. C.: Streptococcus Mucosus (Nov. Spec.?) Pathogenic for Man and Animals, J. M. Research **6**:163, 1901.

association with human lobar pneumonia was first reported by Richardson,[9] who recovered it at autopsy from the lungs in four typical cases. Schottmüller[10] described seven human strains of this organism: one from the pus of a postpartum endometrial abscess, one from the blood and pus in a case of perforative peritonitis, three from the pus in cases of purulent meningitis, one from the blood in a case of pylephlebitis and one from the blood in a case of croupous pneumonia.

When obtained from fresh exudate this organism usually has a much larger capsule than other pneumococci. It excretes larger amounts of its soluble specific carbohydrate into the medium in which it grows.[11] Thus far, it has been found impossible to produce with this organism in animals specific protective antibodies of high titer.[12] Other immunologic reactions of animals to the type III pneumococcus have also been found to be different from those observed with types I and II.[13] Type III is the most common type of pneumococcus found in the normal nasopharynx and in persons with chronic infections of the respiratory tract or of the middle ear.[14]

In relation to the etiology of pneumonia, type III usually ranks third or, with some authors, second among the various types of pneumococci. It may cause as high as 20 per cent of cases of pneumococcic pneumonia (Blake[15]). Cecil, Baldwin and Larsen[16] and more recently Blake[15] have brought out a number of the more important features of

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9. Richardson, O.: Pseudo-Pneumococci in Lobar Pneumonia, J. Boston Soc. M. Sc. **5**:499, 1901.

10. Schottmüller, H.: Die Artunterscheidung der für den Menschen pathogenen Streptokokken durch Blutagar, München. med. Wchnschr. **50**:908, 1903.

11. Dochez, A. R., and Avery, O. T.: The Elaboration of Specific Soluble Substance by Pneumococcus During Growth, J. Exper. Med. **26**:477 (Oct.) 1917.

12. Wadsworth, A. B., and Kirkbride, M. B.: A Note on the Production of Antipneumococcus Sera, J. Exper. Med. **25**:629 (May) 1917.

13. Hanes, I. M.: An Immunological Study of Pneumococcus Mucosus, J. Exper. Med. **19**:38 (Jan.) 1914. Singer, E., and Adler, H.: Immunität gegen Pneumococcus Typus III, Ztschr. f. Immunitätsforsch. u. exper. Therap. **41**:71, 1924. Tillett, W. S.: Studies on Immunity to Pneumococcus Mucosus (Type III), J. Exper. Med. **45**:713 and 1093, 1927; **46**:434, 1927.

14. (*a*) Gundel, M., and Linden, H.: Bakteriologische Untersuchungen an Leichenlungen unter besonderer Berücksichtigung ihrer Bedeutung für das Pneumonieproblem, Ztschr. f. Hyg. u. Infektionskr. **112**:41, 1931. (*b*) Wirth, E.: Der Erreger der akuten Mittelohrentzündung. Beitrag zur Bakteriologie des Streptococcus mucosus, Centralbl. f. Bakt. (Abt. 1) **98**:501, 1926; Die Pneumokokkentypen in der Oto-Rhinologie, ibid. **102**:40, 1927. (*c*) Footnote 3.

15. Blake, F. G.: Observations on Pneumococcus Type III Pneumonia, Ann. Int. Med. **5**:673 (Dec.) 1931.

16. Cecil, R. L.; Baldwin, H. S., and Larsen, N. P.: Lobar Pneumonia: A Clinical and Bacteriologic Study of Two Thousand Typed Cases, Arch. Int. Med. **40**:253 (Sept.) 1927.

the cases of pneumonia associated with this type. These writers pointed out the high incidence in old persons and in persons with chronic debilitating disease as an explanation of the high mortality. Cecil, Baldwin and Larsen also called attention to the higher incidence among elderly women, to the somewhat longer duration of the disease and to the lesser frequency with which recovery by crisis takes place in pneumonia due to type III as compared with that due to other types of pneumococci.

The type VIII pneumococcus also has important features which make it of special importance. This type was first studied by Sugg and Harris as an atypical strain of type III.[17] It is closely related immunologically to type III and in routine typing can be readily confused with the latter because of the high degree of cross-agglutination which may occur in some typing serums.[1b] In a recent study in this laboratory,[18] cross-agglutination and the capacity for cross-protection of mice were also found to exist in the serum of many human patients recovering from pneumonia associated with these two types of pneumococci. In relation to pneumonia, type VIII has been, in our experience,[4a] the most frequent among the types recently separated from the pneumococci previously included in group IV.[1b] It was early observed that the disease caused by this type differs significantly from that due to type III.

The forms of pneumonia caused by these two organisms have been chosen for presentation because they offer a number of features of special interest. They are encountered frequently. They give an interesting contrast with the disease associated with the two commonest types of pneumococci, namely, types I and II. The organisms have frequently been confused because of their cross-agglutination in the serums commonly used for typing. They are closely enough related chemically to cross-agglutinate and to produce high degrees of cross-protection in animals and in man, and yet they produce different disease pictures. The forms of pneumonia due to types I and II will be compared with those due to types III and VIII, and the differences between the forms caused by the latter types will be contrasted.

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17. Sugg, J. Y.; Gaspari, E. L.; Fleming, W. L., and Neill, J. M.: Studies on Immunological Relationships Among the Pneumococci: I. A Virulent Strain of Pneumococcus Which Is Immunologically Related to but Not Identical with Typical Strains of Type III Pneumococci, J. Exper. Med. **47**:917 (June) 1928. Harris, A. L.; Sugg, J. Y., and Neill, J. M.: Studies on Immunological Relationship Among the Pneumococci: II. A Comparison of the Antibody Response of Mice and of Rabbits to Immunization with Typical Type III Pneumococci and to Immunization with a Related Strain, ibid. **47**:933 (June) 1928.

18. Finland, M., and Winkler, A. W.: Response to Infections with Antibody Type III and the Related Type VIII Pneumococcus, J. Clin. Investigation **13**:79 (Jan.) 1934.

PATIENTS STUDIED AND SOURCES OF PNEUMOCOCCI

During the period between Nov. 1, 1929, and May 20, 1933, about 2,000 patients were studied bacteriologically with particular reference to the presence of the various serologic types of pneumococci. In addition to typing serums of types I, II and III, there were available, through the kindness of Dr. William H. Park and Miss Georgia Cooper, serums for types IV to XX throughout the entire period and a total of thirty-two specific typing serums during the last year. Most of the pneumococci obtained during this period were typed with the available serums, and special attention was paid to the two serologically related pairs, types II and V and types III and VIII. Most of the patients had pneumonia or a disease simulating pneumonia. The remainder were patients from whom pneumococci were obtained from various sources in the regular bacteriologic laboratory. In the course of this study, type III pneumococci were obtained, on one or more occasions, from 282 patients, and type VIII, from 125 patients.

The bacteriologic methods have been described elsewhere.[19] Briefly, all specimens of sputum were subjected to routine mouse typing,[20] and on most of them rapid typing was first carried out by the stained slide microscopic agglutination technic described by Sabin.[21] Care was taken to differentiate between the type III and the type VIII organisms by agglutinating each strain in antiserums of both of these types and by repeating the agglutinations with greater dilutions of antiserum in many instances in which cross-agglutination was observed. In the cases of pneumonia an attempt was made to obtain several specimens of sputum and blood. Purulent exudates obtained during life and material obtained at autopsy were cultured.

The determination of the type of organism was made in 60 per cent of the cases of pneumonia from sputum alone, in 5 per cent from blood alone, in 14 per cent from autopsy material alone and in the remaining cases from two or from all three of these sources. The same proportions were found in both the type III and the type VIII cases. In general, all pneumococci obtained from the same patient, either from multiple specimens of the same material or from different materials, were of the same serologic type. A certain number of mixed infections with other types of pneumococci and with other organisms

19. Sutliff, W. D., and Finland, M.: Type I Lobar Pneumonia Treated with Concentrated Pneumococcic Antibody (Felton), J. A. M. A. **96**:1465 (May 2) 1931.

20. Avery, O. T.; Chickering, H. T.; Cole, R. I., and Dochez, A. R.: Acute Lobar Pneumonia, New York, Rockefeller Institute for Medical Research, monograph 7, 1917.

21. Sabin, A. B.: The Microscopic Agglutination Test in Pneumonia, J. Infect. Dis. **46**:469 (June) 1930.

occurred (table 1). Space does not permit a detailed description of these cases. Many of them represented concurrent or consecutive infections. In most instances, however, one of the organisms probably had no relation to the disease.[22] In cases of pneumonia, the type III pneumococcus was found to be associated with other significant organisms more frequently than any other type.

RELATION OF PNEUMOCOCCI OF TYPES III AND VIII TO PNEUMONIA AND TO OTHER DISEASES

The present discussion is concerned primarily with the cases of pneumonia. For purposes of orientation and for comparison all the cases in which pneumococci of types III and VIII were obtained have been classified. An attempt was made to classify the cases of pneumonia according to the character of the pulmonary lesion. All cases

TABLE 1.—*Number of Patients with Type III and Type VIII Pneumonia in Whom Other Significant Organisms Were Obtained*

Organism	Type III Pneumonia	Type VIII Pneumonia
Streptococcus haemolyticus	8	4
Staphylococcus aureus	2	0
Staphylococcus aureus and Streptococcus haemolyticus	2	0
Bacillus mucosus-capsulatus (Friedländer)	3	1
Pneumococcus type I	3	2
Pneumococcus type II	2	0
Pneumococcus type III	..	1
Pneumococcus types V, VIII, XI, XVII and XX (1 each)	5	0
Total mixed infections	25	8

with homogeneous involvement were called lobar pneumonia, and those with patchy consolidation were termed bronchopneumonia. The clinical, roentgenologic and pathologic data were all utilized in making this distinction. In table 2 are shown the number and the percentage of patients from whom each type of organism was isolated who had (1) pneumonia of any kind or empyema, (2) bronchopneumonia, (3) purulent foci of infection without demonstrable pneumonia and (4) conditions showing no particular relation to either pneumonia or focal pneumococcic infection. Similar figures for pneumococci of types I and II are shown for comparison. Both the type III and the type VIII organisms showed a high incidence in cases of focal purulent infections, and both were found in more cases without pneumococcic disease than were types I and II. Furthermore, bronchopneumonia was rare both clinically and at autopsy among the patients from whom types I and II were isolated, whereas it was present in a large proportion of those from

22. Winkler, A. W., and Finland, M.: Antibody Response to Infection with the Newly Classified Types of Pneumococci (Cooper), J. Clin. Investigation **13**: 109 (Jan.) 1934.

whom types III and VIII (particularly the latter) were obtained. The discrepancy between the percentage of cases of bronchopneumonia caused by type VIII found clinically and the percentage found at autopsy is explicable on the basis of the much higher mortality from bronchopneumonia than from lobar pneumonia of this type. This is also true

TABLE 2.—*Relative Frequency with Which Type III and Type VIII Pneumococci Were Isolated from Patients With and Without Pneumonia (Types I and II Included for Comparison)*

Pneumococcus Type	Total Number of Patients	Pneumonia and Empyema		Bronchopneumonia		Focal Infections		No Pneumococcic Disease	
		Number	Per Cent of Type	Number	Per Cent of Type	Number	Per Cent of Type	Number	Per Cent of Type
III	282	225	80	48	17	30	11	27	10
VIII	125	105	84	32	26	11	9	9	7
I	434	410	94	13	3	10	2	14	3
II	219	203	93	10	5	6	3	10	5
Cases with Autopsy									
III	72	64	89	18	22	5	7	3	4
VIII	27	21	78	13	48	3	11	3	11
I	71	67	94	8	11	0	0	4	6
II	36	31	86	3	8	2	6	3	8

TABLE 3.—*Number of Patients with Conditions Other Than Pneumonia from Whom Type III and Type VIII Pneumococci Were Obtained*

	Type III Pneumococcus		Type VIII Pneumococcus	
	Number of Patients	Deaths	Number of Patients	Deaths
Chronic pulmonary diseases	13	3	2	2
Infections of upper respiratory tract	7	0	2	0
No respiratory disease	5	1	1	0
Bacteremia (source unknown)	2	2	4	0
Total nonpneumococcic diseases	27	6	9	2
Otitis media and mastoiditis	15	1	1	0
Meningitis	4	4	3	3
Peritonitis	4	1	4	3
Other purulent foci	7	2	3	0
Total focal infections	30	8	11	6
Total conditions other than pneumonia	57	14	20	8

of type I and type II bronchopneumonia but not of type III, as will appear later.

All of the cases of nonpneumonic conditions, including those without demonstrable pneumococcic infections and those with focal infections, are classified in table 3. The high incidence of infections of the middle ear or mastoid with type III pneumococci, also mentioned by others,[14b] is worthy of note, as is the frequency with which this type of pneumococcus is found in persons with respiratory infections of various kinds.

The remainder of this paper will deal only with the cases in which pulmonary consolidation was found. There were in all 225 cases of type III pneumococcic pneumonia and 105 of type VIII. The condition was fatal in 135 of the former group (a mortality of 60 per cent) and in 38 of the latter group (a mortality of 36 per cent).

RELATION OF AGE TO INCIDENCE AND MORTALITY

In chart 1 are represented the number of patients in each age group who recovered and the number who died. The increasing mortality with advancing age is apparent with both types of pneumonia. The more frequent occurrence of type III pneumonia in the older age groups is at

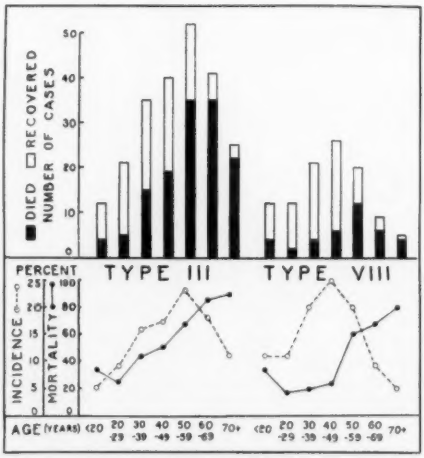

Chart 1.—Percentage incidence and mortality of type III and type VIII pneumonia.

once apparent. The highest incidence of this type was in persons between 40 and 69, 58 per cent of all the patients being of this age group and 11 per cent 70 or older. Among the patients with type VIII pneumonia, 64 per cent were between 30 and 59, and 14 per cent were 60 or older.

In chart 2, the age distribution of the cases of each of these types and also of those of types I and II are plotted together, and the mortality by age groups is similarly shown. From this chart it appears that there is a smaller percentage of younger and a greater percentage of older patients with type III pneumonia than with any of the other types. Pneumonia of types I and II affects the highest percentage of young patients and the fewest old ones, and type VIII pneumonia has an inter-

mediate age distribution. The mortality was found to be lower for type VIII pneumonia in persons of all ages except under 20 years. The mortality from type III pneumonia was higher in most age periods. The mortality from type III pneumonia was similar to that from type II, and type VIII pneumonia caused a mortality similar, in most age periods, to that of type I.

RELATION OF SEX TO INCIDENCE AND MORTALITY

Pneumonia of all kinds, especially lobar pneumonia, is usually found with considerably higher frequency among males than among females.

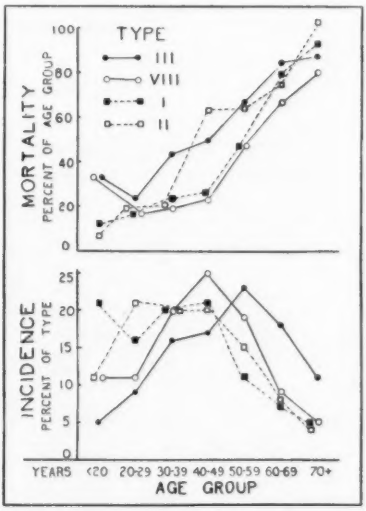

Chart 2.—Comparison between the incidence and mortality, by age groups, of pneumonia of types I, II, III and VIII.

This was found to be true for types III and VIII. There was, however, a wide divergence between the relative percentage of females with pneumonia of types III and VIII and with types I and II. The former groups included 40 and 39 per cent, respectively, of females, whereas only 26 and 14 per cent of the patients with pneumonia of type I and II were females. The distribution of each type of pneumonia between the sexes is shown in chart 3 for all of the cases, for different age groups and for lobar pneumonia and bronchopneumonia. It is seen that the percentage of females increases with age among the patients with type III pneumonia, whereas the highest incidence of females with type VIII pneumonia is among the younger patients. Furthermore,

there are relatively more females than males among the patients with lobar pneumonia of type III and among those with bronchopneumonia of type VIII.

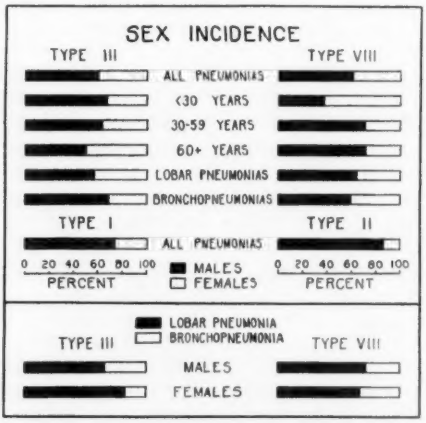

Chart 3.—Sex incidence of type III and type VIII pneumonia and its relation to age and to the character of the pulmonary lesion.

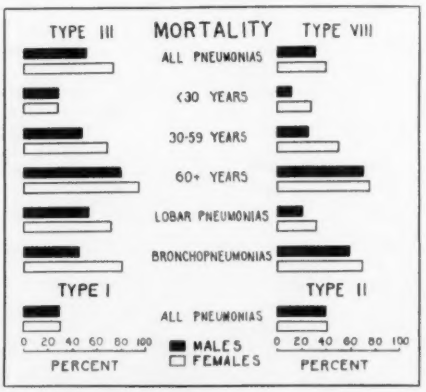

Chart 4.—Mortality from type III and type VIII pneumonia and its relation to sex.

The difference in mortality between the sexes is also of interest (chart 4). There was no significant difference noted among the patients with type I or type II pneumonia. The mortality, however, was higher among the females than among the males both for type III and for type VIII pneumonia. This was true among the patients with type III pneumonia only in the older age groups, in which the incidence was

relatively lower, whereas it was striking in all the patients with type VIII pneumonia except those over 60 years of age, among whom the proportion of females was relatively the lowest.

Thus, as regards sex, type III and type VIII pneumonia have a relatively higher incidence and mortality among females as compared with types I and II. Types III and VIII differ from each other in age distribution and in the incidence of lobar pneumonia and bronchopneumonia. The type III infection has the highest incidence and mortality among elderly females with lobar pnoumonia, and the type VIII infection is relatively more frequent and more fatal among the younger female patients and among the females with bronchopneumonia.

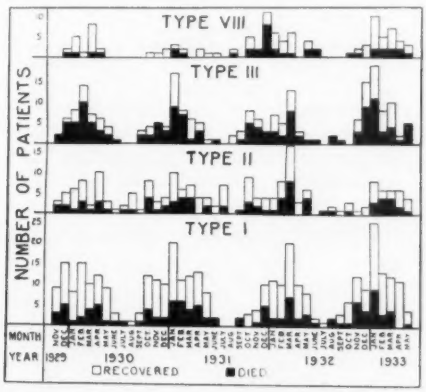

Chart 5.—Monthly incidence of pneumonia of types I, II, III and VIII.

MONTHLY INCIDENCE

The months of highest incidence, as shown in chart 5, were usually the same for pneumonia of types III and VIII as for types I and II. The month in which the largest number of cases occurred differed from year to year. Occasional months showed a high incidence of an individual type of pneumonia without many cases occurring simultaneously among other types.

INCIDENCE OF LOBAR PNEUMONIA AND BRONCHOPNEUMONIA AND RELATION TO MORTALITY

Earlier in this paper attention was called to the uniformity with which types I and II pneumococci are associated with lobar pneumonia. It was also pointed out that, of the three commonest types of pneumococci, type III alone is associated with bronchopneumonia and with conditions other than pneumonia in a large number of cases (table 3).

These facts correlate with the more frequent finding of this type in the mouths of normal persons and also with the higher percentage of mixed infections with this type, as compared with all other types, particularly I and II. The patients from whom type VIII pneumococci were isolated also showed a high percentage of conditions other than pneumonia and an even greater relative incidence of bronchopneumonia than was found among those from whom type III was obtained. It is of interest to compare the two types further with respect to their association with lobar pneumonia and bronchopneumonia and to observe the age distribution and mortality of these clinically different conditions.

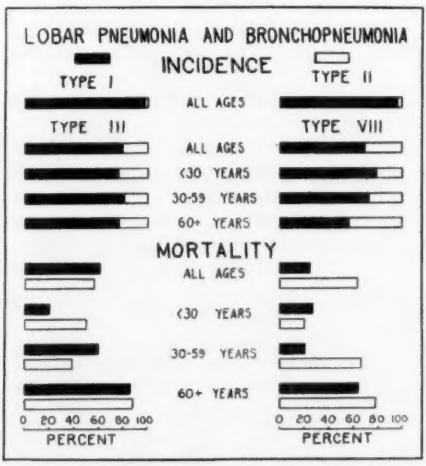

Chart 6.—Incidence and mortality of type III and type VIII lobar pneumonia and bronchopneumonia in different age groups.

In chart 6 it will be seen that while 21 and 30 per cent, respectively, of the type III and type VIII infections were considered "atypical" pneumonia or bronchopneumonia, only a small percentage of the cases of pneumonia of types I and II were diagnosed as bronchopneumonia (3 and 5 per cent, respectively). The incidence of bronchopneumonia was the same in each age group among the patients with type III pneumonia but increased with age among those with type VIII. With respect to mortality also, type III and type VIII pneumonia differed. For all of the type III infections the mortality was the same in patients with lobar pneumonia as in those with bronchopneumonia, although the young and the middle age group varied. The mortality was distinctly higher, however, in the patients with type VIII bronchopneumonia, especially in the middle age group and in the patients 60 or older. The

difference in incidence and mortality among males as compared with females has already been referred to (charts 3 and 4).

Thus the type III and type VIII infections are similar in that a relatively large portion are bronchopneumonia. They differ in that type VIII bronchopneumonia is relatively more frequent in older patients and in females (chart 3). In type III pneumonia the mortality is the same with both types of lesion, whereas bronchopneumonia due to the type VIII pneumococcus is more fatal than lobar pneumonia of the same type, especially in the middle age group.

TABLE 4.—*Primary Conditions in Patients with Secondary Pneumonia* *

	Age, Years	Operation		Cardiac Failure		Bronchial Asthma (Acute)		Sepsis and Acute Infections		Cancer (Terminal)		Fractures		Miscellaneous Conditions†		Total‡	
		R§	D§	R	D	R	D	R	D	R	D	R	D	R	D	R	D
Type III pneumonia	29 and under	3	..	1	..	..	..	2	2	..	..	..	1	..	..	5	3
	30 to 49	3	2	..	..	2	1	1	3	..	..	1	..	..	1[1]	7	7
	50 to 69	6	2	1	9	1	1	..	2	..	5	..	1	..	2[2]	8	22
	70 and over	..	..	1	8	..	..	..	..	..	..	..	..	..	..	1	8
	All.....	12	4	3	17	3	2	3	7	0	5	1	2	0	3	22	40
Type VIII pneumonia	29 and under	2	..	1	..	..	..	..	1	..	..	..	1	..	1[3]	3	3
	30 to 59	1	2	1	1	..	1	..	2	..	1	..	1	..	2[4]	2	10
	60 and over	..	..	..	4	..	..	..	..	..	..	..	..	..	2[5]	0	6
	All.....	3	2	2	5	0	1	0	3	0	1	0	2	0	5	5	19

* Excluding acute infections of the upper respiratory tract (common cold, grip, influenza, acute bronchitis), alcoholism and chronic disease not directly related to the onset of pneumonia.

† The superior figures indicate the following conditions: (1) diabetic gangrene; (2) pernicious anemia (1 case) and cerebral hemorrhage (1 case); (3) dermatitis exfoliativa; (4) hemolytic jaundice (1 case) and pemphigus (1 case); (5) cerebral hemorrhage (1 case) and cirrhosis of the liver and hematemesis (1 case).

‡ Of the cases of type III pneumonia, 30 were lobar pneumonia; of these 18 patients died. Of the cases of type VIII pneumonia, 5 were lobar pneumonia; of these patients 4 died.

§ R indicates recovered; D, died.

SECONDARY PNEUMONIA

Under the term "secondary pneumonia" are classed all cases in which pneumonia developed during a severe acute illness or during an acute episode in the course of a chronic illness. We have excluded, for convenience, all cases of alcoholism, acute or chronic, and all cases in which the pneumonia began during or shortly after a common infection of the respiratory tract, such as common cold, grip, influenza or acute bronchitis. Cases of cardiac disease are included only if there was definite decompensation before the onset of the pneumonia. Postoperative pneumonia is included.

The various diseases during the course of which secondary pneumonia occurred are shown in table 4. The commonest was cardiac failure in old people, in whom this condition and the superimposed pneumonia were usually fatal.

The incidence and mortality of secondary pneumonia, as compared with the remaining cases, which for convenience are termed "primary," are shown in table 5. It is seen that the majority of the cases of bronchopneumonia and only a small percentage of those of lobar pneumonia are secondary. The mortality from secondary pneumonia is apparently the same whether the resulting pulmonary lesion is lobar pneumonia or bronchopneumonia. Among the patients with type III infections, the mortality is the same for all lobar pneumonia, primary and secondary, whereas secondary bronchopneumonia causes more than twice the mortality of primary bronchopneumonia. Type VIII secondary pneumonia causes approximately four times as high a fatality as the primary cases regardless of the anatomic distribution of the pulmonary lesion.

TABLE 5.—*Incidence and Mortality of Secondary Pneumonia*

		Total	Secondary Pneumonia				Primary Pneumonia			
		Number of Cases	Number of Cases	Number of Deaths	Mortality, per Cent	Incidence, per Cent of Type	Number of Cases	Number of Deaths	Mortality, per Cent	Incidence, per Cent of Type
Type III pneumonia	Lobar pneumonia	177	30	18	60	17	147	90	61	83
	Bronchopneumonia	48	32	22	69	67	16	5	31	33
	All	225	62	40	64	28	163	95	58	72
Type VIII pneumonia	Lobar pneumonia	73	5	4	80	7	68	14	21	93
	Bronchopneumonia	32	19	15	79	59	13	5	38	41
	All	105	24	19	79	23	81	19	23	77

PREDISPOSING FACTORS

We shall consider only two groups of predisposing factors, somewhat arbitrarily subdivided. These probably constitute most of the important conditions affecting the occurrence and outcome of pneumococcic pneumonia. Such factors as exposure to cold, to wet or to other unfavorable conditions have not been considered, since they were not frequently encountered.

Alcoholism and Chronic Diseases.—The incidence of these conditions is shown in table 6. Alcoholism and degenerative cardiovascular disease (the cases in which cardiac failure preceded the onset of pneumonia are excluded here) were the most frequent, especially in the fatal cases. Among the patients with acute alcoholism are included only those who were acutely intoxicated at the time of admission or in whom delirium tremens developed during the course of the disease. The mortality among the patients with acute alcoholism was very high, both for type III and for type VIII pneumonia. In all but a small percentage of the entire group there was typical lobar pneumonia. The mortality among these patients was similar to that for all of the patients with pneumonia of the same type.

Antecedent Respiratory Infections.—Acute infections of the respiratory tract, including the common cold, influenza, grip and acute bronchitis, preceded the onset of the pneumonia in about one half of all of the patients for whom a history was obtained, as shown in table 7.

TABLE 6.—*Incidence of Alcoholism and Chronic Diseases Not Directly Related to the Onset of Pneumonia*

Age, Years	Alcoholism: Chronic R*	Alcoholism: Chronic D*	Alcoholism: Acute R	Alcoholism: Acute D	Arteriosclerosis and Hypertension R	Arteriosclerosis and Hypertension D	Chronic Respiratory Disease R	Chronic Respiratory Disease D	Chronic Nonrespiratory Infections R	Chronic Nonrespiratory Infections D	Rheumatic Heart Disease R	Rheumatic Heart Disease D	Cirrhosis of Liver R	Cirrhosis of Liver D	Other Conditions R	Other Conditions D	Total R	Total D
Type III Pneumonia																		
29 and under	1	1	1	1	..	..	2	2	1	..	1	1	..	..	..	..	6	5
30 to 49	4	4†	1	7†	1	..	1	2	5	1	1	1	..	3	1	1	14	17
50 to 69	3†	5	3‡	8	3	11	2	5	1	3	..	..	1	..	1	5	12	37
70 and over	1	..	..	..	..	6	1	2	..	1	..	1	..	..	1	1	3	11
All.....	9	10	5	16	4	17	6	11	7	5	2	3	1	3	3	7	35	70
Type VIII Pneumonia																		
29 and under	..	..	..	..	..	..	5	..	1	1	..	..	..	..	1	1	7	2
30 to 59	9§	2	3‖	3¶	1	4	4	1	..	..	..	..	..	..	1	2	14	10
60 and over	..	1	..	..	1	..	1	..	..	..	..	..	..	..	..	..	2	1
All.....	9	3	3	3	2	4	10	1	1	1	0	0	0	0	2	3	23	13

* R indicates recovered; D, died.
† Including 1 with cirrhosis of the liver.
‡ Including 1 with diabetes.
§ Including 1 with secondary anemia and 1 with chronic bronchitis.
‖ Including 2 with chronic respiratory disease.
¶ Including 1 with hypertension and 1 with chronic bronchitis.

TABLE 7.—*Incidence and Mortality of Cases of Pneumonia in Which a History Regarding Antecedent Respiratory Infections Was Obtained*

	Total Number of Cases	Cases with Antecedent Respiratory Infections: Number of Cases	Incidence, per Cent	Number of Deaths	Mortality, per Cent	Cases Without Antecedent Respiratory Infections: Number of Cases	Incidence, per Cent	Number of Deaths	Mortality, per Cent
Type III pneumonia									
Lobar pneumonia.....	157	78	50	45	59	79	50	44	56
Bronchopneumonia.....	37	14	38	4	28	23	62	14	61
All cases.....	194	92	47	49	53	102	53	58	57
Type VIII pneumonia									
Lobar pneumonia.....	66	38	58	7	18	28	42	8	28
Bronchopneumonia.....	29	14	48	6	43	15	52	11	73
All cases.....	95	52	55	13	25	43	45	19	44

They were somewhat more common among the patients with type VIII pneumonia (55 per cent of those for whom a history could be obtained) than among those with type III (47 per cent). They were slightly more frequent in lobar pneumonia than in bronchopneumonia of either type. Although this is not shown in the table, they were found to be slightly more common in the younger patients with each type of pneu-

monia. Among the patients with bronchopneumonia the mortality was much higher when there was no history of an antecedent respiratory infection than when such an infection had occurred. This is probably accounted for by the fact that many of the cases of bronchopneumonia without respiratory infections were secondary.

CLINICAL FINDINGS

It was pointed out by Blake [15] that the symptoms and course of pneumonia caused by the type III pneumococcus are similar to those of pneumonia caused by other types. This we have found, in general, to be true for both type III and type VIII pneumonia. Furthermore,

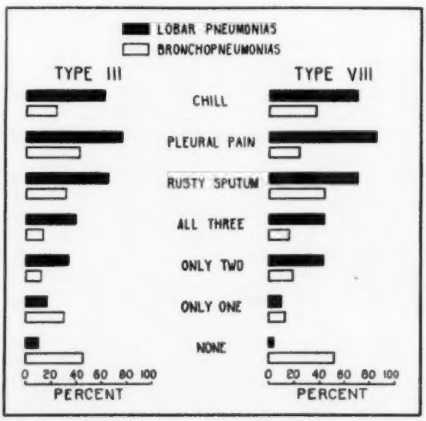

Chart 7.—Incidence of three cardinal symptoms of pneumonia in type III and type VIII lobar pneumonia and bronchopneumonia.

the symptomatology appears to be more closely related to the anatomic lesion than to the etiologic type.

Mode of Onset.—The onset was sudden in the majority of cases of lobar pneumonia and gradual in most of the cases of bronchopneumonia of both types. A sudden onset occurred in 72 per cent of the cases of lobar pneumonia of type III and in 81 per cent of those of type VIII, but only in 40 and 33 per cent, respectively, of the cases of type III and type VIII bronchopneumonia. The two most common initial symptoms in lobar pneumonia were chill and pain in the chest, one or both of these ushering in the disease in 69 per cent of the cases of type III lobar pneumonia and in 74 per cent of those of type VIII. No single symptom characterized the onset of bronchopneumonia, the most common initial symptom being fever, cough or dyspnea, each of which occurred at the onset in less than one fourth of the cases.

Cardinal Symptoms.—The cardinal features of lobar pneumonia characterized the picture of this disease, as contrasted with that of bronchopneumonia, in both the type III and type VIII cases. In chart 7 is indicated diagramatically the frequency with which three of the cardinal symptoms, namely, chills, pain in the chest and rusty or blood-tinged sputum, were present separately or in combination in the cases of lobar pneumonia and bronchopneumonia of each type. Two or all three of these symptoms were present in 73 per cent of the cases of type III lobar pneumonia and in 85 per cent of those of type VIII,

TABLE 8.—*Extent of Pulmonary Lesion*

	Lobar Pneumonia																				Broncho-pneumonia					
	Right Lung										Left Lung						Bilateral									
	Lower		Middle		Upper		Middle and Lower		Upper and Middle		Entire		Lower		Upper		Entire		2 Lobes		3 or More Lobes		Mostly Right		Mostly Left		Bilateral	
Age, Yrs.	R*	D*	R	D	R	D	R	D	R	D	R	D	R	D	R	D	R	D	R	D	R	D	R	D	R	D	R	D
Type III Pneumonia																												
19 and under	5	..	..	..	..	..	..	..	..	..	..	..	2	..	..	..	..	..	..	..	..	..	1	1	..	..	..	3
20-29	1	1	1	..	1	..	2	1	..	..	2	..	5	1	..	..	..	..	1	..	..	..	..	..	1	..	2	..
30-39	5	3	..	..	1	2	1	2	1	2	1	..	5	1	..	..	1	1	2	1	..	..	1	..	..	..	2	2
40-49	3	5	..	..	6	3	1	..	..	1	1	2	3	1	1	..	..	..	3	..	1	1	..	2	..	3	2	
50-59	4	3	..	..	..	5	..	2	..	3	1	4	3	5	1	1	1	..	1	5	..	2	3	1	..	..	3	4
60-69	0	2	1	1	..	2	..	..	..	1	1	4	2	2	1	3	..	4	..	6	..	2	..	3	..	..	1	5
70 and over	1	3	..	..	..	2	..	..	..	1	..	2	1	1	..	1	..	..	..	5	..	1	..	2	..	..	1	4
All	19	17	2	1	8	14	4	5	1	8	6	12	21	11	3	5	2	5	1	22	1	6	6	7	3	0	12	20
Type VIII Pneumonia																												
19 and under	1	..	..	..	1	..	..	..	..	..	1	..	2	..	..	1	..	..	..	2	1	..	..	..	1	..	2	1
20-29	2	..	..	..	2	..	..	..	..	..	2	..	1	..	..	..	..	1	1	..	..	1	..	..	..	..	1	..
30-39	8	1	..	..	..	..	..	..	..	..	..	..	3	..	1	..	..	..	1	..	..	..	1	1	..	..	2	2
40-49	6	3	..	..	5	1	..	..	1	..	1	..	4	1	..	..	..	..	1	..	..	..	..	..	1	..	1	1
50 and over	1	2	..	..	1	..	..	..	..	..	2	..	3	3	..	..	..	..	..	1	..	1	2	4	..	1	1	10
All	18	6	0	0	9	1	0	0	1	0	6	0	13	4	1	1	0	1	3	3	1	2	3	5	2	1	7	14

* R indicates recovered; D, died.

as contrasted with only 25 and 35 per cent, respectively, of the cases of bronchopneumonia of these types.

Extent of Consolidation.—The frequency with which various lobes were involved in persons of different age groups is shown in table 8. In general, the lesion tended to be localized in one lobe or in one lung in the young patients with type III lobar pneumonia. Otherwise, no relation was observed between the patient's age and the location of the lesion. There was a direct relationship between the extent of involvement and the mortality. The right lung was involved about twice as frequently as the left. Among the patients with type III lobar pneumonia, involvement of the upper lobe was associated with a higher mortality, but this was not true among the patients with type VIII lobar pneumonia. Among the patients with bronchopneumonia, the lesion was

bilateral in two thirds of the cases of each type. When, however, the lesion was largely limited to one side, it was more commonly on the right.

Duration of Disease and Mode of Termination.—We have arbitrarily defined as crisis a permanent drop in temperature to 100 F. and obvious coincident clinical improvement occurring within twenty-four hours. If this change occurred over a longer period, the day that the temperature first dropped to 101 F. was considered as the day when lysis took place. By these criteria, only 33 per cent of the patients with type III lobar pneumonia and 27 per cent of those with type VIII who recovered and even fewer of the patients with bronchopneumonia showed recovery by crisis. Almost all of the patients who recovered by crisis were under 50 years of age.

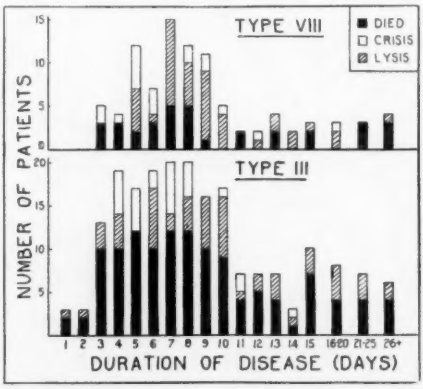

Chart 8.—Duration and outcome in type III and type VIII pneumonia.

The duration of the disease and the mode of recovery in all of the cases of pneumonia are shown graphically in chart 8. Seventy-three per cent of the cases of type III pneumonia in which the duration of the disease could be determined terminated before the end of the tenth day, and 70 per cent of those of type VIII pneumonia terminated before the end of the ninth day. Termination by crisis in type III pneumonia usually occurred before the eighth day. About 10 per cent of the cases of each of these two types of pneumonia lasted longer than fifteen days.

Relation of Leukocyte Count to Outcome.—The high mortality among patients with pneumonia associated with leukopenia has frequently been noted. It was thought to be of interest to compare the leukocyte level in type III and type VIII pneumococcic pneumonia in different age groups. The frequency with which different levels of the blood leukocytes were observed is shown in table 9. In spite of the

striking difference in mortality between these two types of pneumonia, the frequency with which different white blood cell levels were encountered was strikingly similar. Leukopenia was infrequent in both of these types. All but 1 of the patients with less than 5,000 white corpuscles per cubic millimeter of blood died; otherwise no striking relationship existed between the level of the leukocytes and the outcome. Leukocyte counts over 30,000 were infrequent. The mortality in such cases was slightly higher than the average. Only slight differences were observed among the different age groups, leukopenia being relatively uncommon in the young patients and high leukocyte counts slightly less common in the very old patients.

TABLE 9.—*Leukocytosis and Mortality in Different Age Groups*

		Leukocytes per Cubic Millimeter									
		Less Than 5,000		5,000 to 10,000		10,000 to 20,000		20,000 to 30,000		30,000 and Over	
	Age, Years	R*	D*	R	D	R	D	R	D	R	D
Type III pneumonia	29 and under	0	1	1	2	11	3	5	0	3	1
	30 to 49	0	2	3	4	20	17	6	3	1	1
	50 to 69	0	2	5	4	8	24	3	12	1	4
	70 and over	0	1	0	4	2	10	0	2	0	2
	All	0	6	9	14	41	54	14	17	5	8
	Mortality, per cent	100		61		57		55		63	
	Incidence, per cent	4		14		57		18		8	
Type VIII pneumonia	29 and under	0	0	3	1	7	1	6	3	1	1
	30 to 49	1	4	5	1	19	5	10	1	4	0
	50 and over	0	1	4	3	6	9	1	1	0	2
	All	1	5	12	5	32	15	17	5	5	3
	Mortality, per cent	83		29		32		23		37	
	Incidence, per cent	6		17		47		22		8	

* R indicates recovered; D, died.

Complications.—Purulent complications were observed during life in about 10 per cent of the cases of each type. In the type III cases, most of these complications were in association with lobar pneumonia, whereas one half of those observed in the type VIII cases were associated with bronchopneumonia. The number of the various complications observed is shown in table 10.

BACTEREMIA

Blood cultures were made on one or more occasions during life in 131 patients with type III and in 68 patients with type VIII pneumococcic pneumonia. Positive cultures were obtained in 46 of the former, an incidence of 35 per cent, and in 21 of the latter, an incidence of 31 per cent. No instance of recovery was observed in any patient with type III pneumococcic bacteremia,[22a] whereas only 43 per cent of the

22a. Since this paper was submitted we have observed 2 patients, aged 46 and 62, respectively, who had lobar pneumonia and type III pneumococcus bacteremia and recovered without complications.

patients with type VIII bacteremia died. The mortality in patients with sterile blood cultures was 34 per cent and 21 per cent among the patients with type III and type VIII pneumonia, respectively.

Pour plates and colony counts were made for over one half of the patients. Among 7 patients with type VIII pneumococcic bacteremia for whom pour plates were made, 4 showed less than 10 colonies per cubic centimeter of blood, and the remaining 3 showed 11, 24 and 2,000 colonies, respectively. Among 26 patients with type III bacteremia in whom the extent of invasion of the blood was quantitated, 6 showed no colonies on plates (that is, only the broth culture was positive), 9 showed less than 20 colonies per cubic centimeter and the remaining

TABLE 10.—*Incidence of Complications* (Diagnosed During Life)*

	Type III Pneumonia		Type VIII Pneumonia	
	Recovered	Died	Recovered	Died
Empyema	3	9	6	2
Pulmonary abscess and empyema	..	2	..	1
Pericarditis	..	2	..	..
Meningitis	..	2†	..	2
Otitis media	1	1	..	..
Sterile pleural effusions	1	6	3	1
Miscarriage	..	1	..	1
Jaundice	6	17‡	4	2
Atelectasis	2	..	2	1
Conjunctivitis	..	..	1	..
Hemoptysis	..	..	..	1
Pulmonary infarcts§	1	1	..	..
Pneumothorax and jaundice	1	..	..	..

* Not including mixed infections with other organisms.
† One patient had otitis media also.
‡ One patient had pneumothorax also.
§ Patients with rheumatic heart disease.

11 showed 75 or more colonies. In 5 of the latter, more than 1,000 colonies per cubic centimeter were observed in the later cultures.

The relation of bacteremia to age, to the outcome and to the stage of the disease is shown for type III pneumonia in chart 9 and for type VIII in chart 10. In type III pneumonia, death in young patients was usually associated with bacteremia, and the incidence of bacteremia among patients who died diminished with advancing age. The incidence of bacteremia increased during the course of the fatal cases, but showed a decline after the fifteenth day of the disease. In type VIII pneumonia, bacteremia occurred with increasing frequency among patients with fatal cases in advancing age groups, whereas, among the patients who recovered it was frequent only in the middle age group. Conversely, the mortality was relatively higher in patients with bacteremia in the older age group. In the fatal cases the highest incidence of bacteremia occurred before the ninth day, after which the blood culture was usually negative.

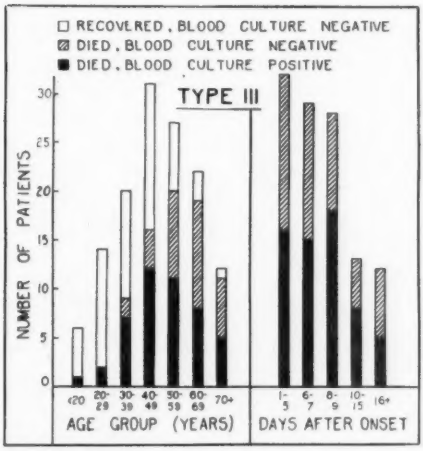

Chart 9.—Bacteremia in type III pneumonia in relation to the age of the patients and the outcome (left) and in relation to the duration of the disease in fatal cases (right).

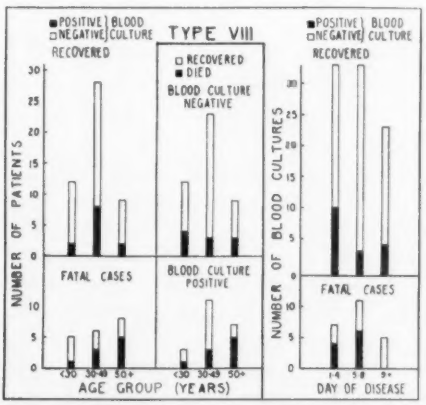

Chart 10.—Bacteremia in type VIII pneumonia in relation to the age of the patients and the outcome (left) in relation to the mortality among patients with positive blood cultures and among those with negative blood cultures (center) and in relation to the duration of the disease in patients who recovered and in those who died (right).

In table 11 are shown the results of blood cultures in a group of 14 cases of type III pneumonia in which both positive and negative cultures were obtained. The number of cases is small, but they indicate that bacteremia may develop late and may be transient and that death may ensue in spite of the fact that bacteremia has subsided.

Invasion of the blood by other organisms was observed in 5 patients with type III pneumonia. One of these had type XI pneumococci in the blood on two occasions and subsequently recovered. Another patient who died had type I pneumococci in the blood twice and both type I and type III pneumococci in the sputum. A third patient showed type I

TABLE 11.—*Relation of Bacteremia to the Course of the Disease in Patients with Type III Pneumonia in Whom Both Positive and Negative Blood Cultures Were Obtained*

		Results of Blood Cultures* Day of Disease																Autopsy, Hours Post
Case	Age, Yrs.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	Mortem
1	62	..	..	..	..	..	..	..	+	0	..	..	D	..	..	..	..	..	..
2	57	..	..	..	..	..	..	..	..	..	..	..	..	+	..	0	..	0D	..
3	44	..	..	..	..	..	..	..	0	+	+0	D	..	..	..	..	..	..	..
4	64	..	..	..	..	..	..	0	0	0	..	0	..	..	..	D+	..	..	4
5	45	..	..	..	..	..	0	..	+	..	+	D	..	..	..	..	..	..	..
6†	55	..	..	..	+	+	++	+D0	..	..	..	..	..	..	..	..	..	..	2
7	71	..	..	..	..	0	+	..	D	..	..	..	..	..	..	..	..	..	..
8	54	..	..	0	..	+	D	..	..	..	..	..	..	..	..	..	..	..	..
9‡	63	0D	+	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	16
10	39	..	..	..	0	..	+	..	D+	..	..	..	..	..	..	..	..	..	6
11‡	60	..	..	..	..	..	0	..	+	D	0	..	..	..	..	..	..	..	12
12	21	..	..	..	..	..	0	+	..	..	D	..	..	..	..	..	..	..	..
13	49	..	..	..	..	0	..	..	0	+	D	..	..	..	..	..	..	..	..
14§	43	..	..	..	..	..	..	..	..	..	..	..	I I I	+D	..	..	..	..	..

* 0 indicates negative blood culture; +, blood culture positive for Pneumococcus type III; D, died; I, blood culture positive for Pneumococcus type I.

† Treated with homologous convalescent serum.

‡ Bronchopneumonia.

§ Treated with Felton's serum (type I and II antibody solution). This patient had type I and type III pneumococci in the sputum.

pneumococci and probably no type III organisms in the blood on three occasions within the same day, and the fourth examination showed only type III pneumococci (case 14, table 11). This patient was treated with Felton's serum. Both type I and type III pneumococci were recovered from the sputum and from the fluid obtained by puncture of the lung post mortem. Two other patients with type III pneumococci in the sputum showed hemolytic streptococci in the blood, one before death and the other in the heart's blood post mortem.

One of the patients with type VIII pneumonia had hemolytic streptococci, and another had Friedländer bacilli, in the heart's blood at autopsy. Both of these patients showed type VIII pneumococci in the lungs. A third patient had type VIII pneumococci in the sputum, but only hemolytic streptococci were recovered from the heart's blood and lungs at autopsy.

POSTMORTEM OBSERVATIONS

The gross and microscopic observations in the cases that came to autopsy were reviewed, and a summary of the important findings is presented in table 12. The high incidence of bronchial involvement in type III lobar pneumonia is of interest. In most instances the mucosa of the trachea, bronchi and bronchioles was thickened and inflamed and contained an inflammatory exudate which, for the most part, was thick and mucopurulent. In many instances, however, a frank purulent exudate was observed. Empyema was noted in the type III cases only in association with lobar pneumonia. The amount of purulent exudate in the pleural cavity varied, being less than 100 cc. in 4 cases and over

TABLE 12.—*Summary of Postmortem Observations Relating to Lungs and Adjoining Structures*

	Type III		Type VIII	
	Lobar Pneumonia	Broncho-pneumonia	Lobar Pneumonia	Broncho-pneumonia
Number of cases	46*	18	8	13
Tracheitis and bronchitis	27	12	2	5
Serofibrinous effusion	7†	4†	2	1
Empyema	11	0	2	1
Abscesses of lung	15‡	1§	1	1
Pericarditis	3	0	0	0
Meningitis	0	1	1	1
Vegetative endocarditis	1	0	0	0
Pulmonary involvement:				
Limited to one lobe	13	0	3	0
Unilateral, in more than one lobe	18	5	1	2
Bilateral	15	13	4	11
Shiny mucoid cut surface	10	1	0	0

* Includes one patient that had patchy involvement of one lung and lobar consolidation in the other.
† Two were bilateral.
‡ Three were observed only microscopically.
§ Diagnosed microscopically.

500 cc. in 4; the exudate was unilateral in every instance. The serofibrinous effusions also varied in amount. In 1 case of type III lobar pneumonia there was 500 cc. in one pleural cavity and 1,400 cc. in the other; in the remaining cases there was 200 cc. or less. In all of the cases of type III bronchopneumonia, the pleural cavity contained 250 cc. or more. The most significant finding, however, was the high incidence of parenchymatous destruction and abscess formation in the type III lobar pneumonia. This was found in one third of these cases, an incidence much higher than has been observed in any other group. A shiny, mucoid appearance of the cut surface, thought to be characteristic of type III as contrasted with other types of lobar pneumonia, was not so frequent as was expected, although the type III pneumococcus was obtained directly from the lungs in all but 5 of the cases.

Most of the findings in the cases of type III pneumonia are consistent with the longer duration of the disease which has been noted. In the early description of Richardson,[9] these findings, coupled with

the scarcity of organisms and the failure to find the usual characteristic pneumococci, were interpreted as indicating that the type III organisms, which he found and described under the names "Streptococcus mucosus" and "pseudopneumococci," were probably late secondary invaders.

COMMENT

This description of two different diseases, caused by related organisms that can be differentiated only by bacteriologic methods, is of practical importance as well as of theoretical interest. The facts presented are useful in diagnosis and in prognosis and are of potential value in epidemiology and in therapy.

In regard to prognosis, the data indicate clearly the striking differences in the death rate associated with pneumonia due to these two organisms.

As to diagnosis, it is probable that a certain number of cases caused by type VIII pneumococci have been classified among those of type III pneumonia because of the rather marked cross-agglutination that may occur with some of the more reactive strains of these types. One would expect that the separation of such cases of type VIII pneumonia, having a lower death rate, from the cases of type III pneumonia would leave a group that would collectively appear more severe than the disease previously associated with the type III pneumococcus.

That this may have occurred is shown by the information available with regard to bacteremia. While most observers have found the death rate in cases of pneumonia with type III pneumococcic bacteremia to be high, they have noted recoveries with varying frequency.[23] Among the cases reported here, 100 per cent of those with type III bacteremia ended fatally. It seems possible that some of the patients with pneumonia reported by others to have recovered following type III pneumococcic bacteremia really had type VIII infections.

Some strains of type VIII pneumococci were probably also included among the organisms used in some attempts to produce potent type III antiserums, although these strains were sometimes recognized as atypical.[12] Such errors did not account for the major difficulties encountered in this work, as most of the organisms used gave the reactions characteristic of the typical strains of type III pneumococci.

The more careful recognition of the etiologic agents in cases of bronchial and atypical pneumonia may help in elucidating some of the factors responsible for the occurrence of these rather poorly understood diseases. It is well known that such cases are common and that they are given less attention than their frequency and importance deserve.

23. Warr, O. S., and Alperin, J.: Lobar Pneumonia: A Report of 2,039 Cases, Ann. Int. Med. **6**:1474 (May) 1933.

It is especially important to understand the reasons for the occurrence of bronchial and secondary pneumonia in hospitalized patients and in others, since the whole course is frequently observed by the physician. Such an understanding depends, in large part, on a knowledge of the strains of bacteria, usually pneumococci, that are involved and on the determination of their source. This epidemiologic aspect of secondary and bronchial pneumonia will be furthered by the accurate determination of types of pneumococci.

The differentiation of serologically specific strains of related organisms also has potential value in regard to therapy. Thus far, the significant successes in combating pneumococcic infections have been obtained with strictly type-specific agents. This has been true with respect to the vaccines used in prophylaxis [24] and the serum used in the treatment of lobar pneumonia and with respect to the enzymes used in curing animals of experimental infections with type III pneumococci.[25] In order to use any of these methods of approach, one must first recognize the specific nature of the causative agent of the disease.

SUMMARY

A review is presented of the major findings in a consecutive series of 282 patients from whom the type III pneumococcus was obtained and 125 patients from whom the serologically related type VIII pneumococcus was obtained at the Boston City Hospital between November, 1929, and May, 1933. In particular, 225 cases of type III pneumococcic pneumonia were compared with 105 cases of type VIII pneumococcic pneumonia.

A large proportion of type III and type VIII pneumococci were recovered from patients who did not have pneumonia. Type I and type II pneumococci were comparatively rare in patients without pneumonia.

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24. Lister, F. S.: An Experimental Study of Prophylactic Inoculation Against Pneumococcal Infections in the Rabbit and in Man, Publications of the South African Institute for Medical Research, no. 8, 1916. Lister, F. S.: Prophylactic Inoculation of Man Against Pneumococcal Infections, and More Particularly Against Lobar Pneumonia, Publications of the South African Institute for Medical Research, no. 10, 1917. Cecil, R. L., and Austin, J. H.: Results of Prophylactic Inoculation Against Pneumococcus in 12,519 Men, J. Exper. Med. **28**:19 (July) 1918. Cecil, R. L., and Vaughan, H. F.: Results of Prophylactic Vaccination Against Pneumonia in Camp Wheeler, ibid. **29**:457 (May) 1919.

25. Avery, O. T., and Dubos, R.: The Protective Action of a Specific Enzyme Against Type III Pneumococcus Infection in Mice, J. Exper. Med. **54**:73 (July) 1931. Goodner, K.; Dubos, R., and Avery, O. T.: The Action of a Specific Enzyme upon the Dermal Infection of Rabbits with Type III Pneumococcus, ibid. **55**:393 (March) 1932.

About one fifth of the pulmonary infections with the type III pneumococcus and one third of those with type VIII were bronchopneumonia, whereas only 3 per cent of the infections due to the type I pneumococcus and 5 per cent of those due to type II were bronchopneumonia.

Mixed infections with other significant organisms were more frequent in type III and type VIII pneumococcic pneumonia (especially the former) than in any other type.

The proportion of females among the patients with type III and type VIII pneumonia was two or three times as great as among the patients with pneumonia of types I and II. Furthermore, the mortality in the latter types was the same for both sexes, whereas it was appreciably higher among females with both type III and type VIII pneumonia.

Bronchopneumonia was more frequent among the patients with type VIII than among those with type III pneumonia. The mortality among those with type III infections was the same for bronchopneumonia as for lobar pneumonia. Type VIII bronchopneumonia caused a mortality more than twice as high as that of lobar pneumonia of the same type.

The majority of cases of bronchopneumonia of both types were secondary and began during the course of some other serious illness or following an operation. Only a small percentage of the cases of lobar pneumonia were secondary. The mortality in secondary pneumonia was from two to four times as high as in primary pneumonia, except in secondary lobar pneumonia due to the type III pneumococcus. In the latter cases, the mortality was the same as in primary pneumonia of the same type.

Alcoholism and chronic disease were common predisposing factors in both type III and type VIII pneumonia. Chronic infections of the respiratory tract and degenerative cardiovascular disease were the most frequent. Acute infections of the respiratory tract preceded the onset in one half of the cases of both types. Except in type III lobar pneumonia, the mortality was lower in patients who had an antecedent respiratory infection than in those who did not.

The clinical features in type III and type VIII pneumonia were similar to those found in types I and II. Sudden onset, chill, pleural pain and rusty sputum were the predominant features among the patients with lobar pneumonia of both types and were relatively uncommon among the patients with bronchopneumonia.

Leukopenia was rare in both types of pneumonia. It was significant only when the level of the leukocytes dropped below 5,000 per cubic millimeter of blood.

The duration of the disease was somewhat longer in type III than in type VIII pneumonia. Recovery by crisis was relatively uncommon in both types. It occurred more frequently in young persons who recovered early.

Bacteremia was present in about one third of the cases of both types. All of the patients with pneumonia and type III pneumococcic bacteremia died; 43 per cent of those with type VIII pneumococcic bacteremia died. The degree of the invasion of the blood was greater in type III pneumonia.

The most significant postmortem observation was the finding of areas of necrosis in the consolidated areas in one third of the cases of type III lobar pneumonia.

These two types of pneumococci produce diseases which differ, in similar ways, from pneumonia caused by types I and II but which exhibit striking differences from each other. The importance of differentiating these organisms has been discussed.

ACUTE STREPTOCOCCUS VIRIDANS ENDOCARDITIS

REPORT OF FOUR CASES, WITH AUTOPSY OBSERVATIONS IN TWO

I. W. HELD, M.D.
AND
A. ALLEN GOLDBLOOM, M.D.
NEW YORK

The fact that Streptococcus viridans, usually a nonpathogenic organism regularly residing as a saprophyte in the teeth, tonsils, vagina and other organs, can be the cause of fatally terminating endocarditis was discovered by Schottmueller.[1] This author was the first to demonstrate that in order to cause endocarditis this organism must implant itself on a previously diseased or congenitally deformed valve, the order of frequency in case of a diseased valve being a rheumatic valve, more rarely a syphilitic valve and still more rarely an arteriosclerotic valve. When Schottmueller recognized that this form of endocarditis, which he still believes can be caused only by Str. viridans, almost always has a protracted course, he named it "endocarditis lenta."

Libman [2] and his associates, notably Celler,[3] working in this country, have found, however, that similar pathologic changes in a chronically diseased valve, giving rise to a like clinical course, can be caused by organisms other than Str. viridans, principally by pneumococci, the influenza bacillus, gonococci, staphylococci, hemolytic streptococci and members of the genus Proteus. Therefore, Libman named the disease "subacute bacterial endocarditis." As his work has been confirmed by many authors, both in the United States and abroad, this name has continued in use.

Although subacute bacterial endocarditis is frequently encountered, acute Str. viridans endocarditis occurs so seldom that even such observers as Schottmueller, Bingold,[4] Blumer,[5] Thayer [6] and others have

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From the Medical and Pathological Departments, Beth Israel Hospital.

1. Schottmueller, H.: Die Artunterscheidung der für den Menschen pathogenen Streptokokken durch Blutagar, München. med. Wchnschr. **50**:849 and 909, 1903; Endocarditis lenta, ibid. **57**:617, 1910.

2. Libman, E.: Endocardial Lesions of Subacute Bacterial Endocarditis, Am. J. M. Sc. **144**:313, 1912.

3. Libman, E., and Celler, H. L.: Etiology of Subacute Infective Endocarditis, Am. J. M. Sc. **140**:516 (Oct.) 1910.

4. Bingold, K.: Septische Erkrankungen, Neue deutsche Klin. **9**:689, 1932.

5. Blumer, G.: Subacute Bacterial Endocarditis, Medicine **2**:105 (May) 1923.

6. Thayer, W. S.: Studies on Bacterial (Infective) Endocarditis, Johns Hopkins Hosp. Rep. **22**:1, 1926.

reported very few cases. Because of this rarity, we believe that a description of four cases that have recently come under our observation will be of interest.

Whatever organism causes subacute endocarditis, the existing pathologic process in the valve to a large extent determines the clinical picture. That is, the excrescences on the valve serve as a focus of infection, giving rise to protracted illness. In the acute cases, on the other hand, although the valve shows evidences of polypi and ulceration—sometimes more ulceration than polypous excrescences—the picture is primarily that of true septicemia.

The salient symptoms and signs of typical subacute bacterial endocarditis are well known; those of acute Str. viridans endocarditis are less familiar. We believe that the picture of the latter condition will best emerge if, in addition to stating the findings in our cases, we preface these by a somewhat detailed outline of the features of subacute bacterial endocarditis, which will make the differences between the two conditions more readily apparent.

SUBACUTE BACTERIAL ENDOCARDITIS

An outstanding feature of subacute bacterial endocarditis, and one that immediately distinguishes it from acute Str. viridans endocarditis, is that the temperature curve is not characteristic; in fact, the more protracted the course of the disease, the less tendency there is to a septic type of temperature. The temperature may be transiently very high, with the patient extremely euphoric, as in typhoid, but it is far more often subfebrile. The blood pressure is not elevated as a rule. The pulse is seldom rapid until the terminal stage of the disease, when multiple emboli begin to occur. In nearly all cases there is secondary anemia—the café au lait anemia described by Libman. Tenderness over the sternum is generally present on percussion. Clubbing of the fingers, particularly red clubbing, is an important symptom. Janeway's nodes on the tips of the phalanges or on the tips of the toes, extremely tender to touch, are diagnostic. White-centered petechiae in the conjunctivae are also diagnostic.

The patient is seldom heart-conscious, all cardiac symptoms being in the background. There is rarely any cardiac decompensation, because persons in whom there is decompensation rarely have subacute bacterial endocarditis. As a rule, there is neither fibrillation nor any other form of arrhythmia. A murmur is always present but is changeable in character; because of the associated anemia it is sometimes wrongly interpreted as a hemic murmur. As this form of endocarditis implants itself most often on a previously diseased aortic valve (aortic insufficiency), there is almost always a characteristic diastolic murmur; when such a

murmur is heard, the diagnosis is established with absolute certainty, no matter what the rest of the clinical or the hematologic picture may be.

Emboli are common. Small or large pieces of the polypous excrescences break off and are carried through the arterial stream to distant parts of the body, causing obliteration of capillaries, arterioles or even large arteries. In the capillaries and small arterioles, aneurysmal dilatation often takes place, the rupture of small aneurysms giving rise to hemorrhage wherever the rupture occurs, for instance, into the gastric cavity or into the subarchnoid space or some other portion of the brain. If the process occurs in the brain, there are outstanding symptoms of hemiplegia, meningitis or pachymeningitis. If the emboli lodge in the small peripheral vessels of the extremities, the symptoms simulate those of Raynaud's disease. Occasionally emboli occur in large vessels, such as the tibial vessels or the mesenteric or coronary vessels, completely obstructing the flow of blood to adjacent tissues, with resulting necrosis and gangrene of those tissues. Larger emboli may cause a saddle-shaped thrombus at the bifurcation of the aorta, obliterating the aorta. In protracted cases, there may be diffuse embolic nephritis instead of the focal embolic nephritis that is present in from 60 to 70 per cent of all cases. The fatal termination of such cases is usually the result of renal insufficiency, but no matter how marked the uremia, pericarditis is never present and the blood pressure is, as a rule, not elevated.

Examination of the peripheral blood, particularly from the ear, often shows macrophages. These are encountered in subacute bacterial endocarditis more than in any other severe infection.

In some cases, in which the predominant disturbances are in the hematopoietic system, there is marked secondary anemia, and the blood picture is similar to that of subleukemic leukemia, with from 15 to 20 per cent myelocytes and myeloblasts. In these cases the spleen is enormously enlarged, so that differential diagnosis between subacute bacterial endocarditis and myeloblastic leukemia is exceedingly difficult. In rare cases, the clinical picture simulates Banti's complex; that is, there is an immensely enlarged, hard spleen, and sometimes an enlarged liver, a hemorrhagic diathesis, leukopenia and mononucleosis are observed.

ACUTE STR. VIRIDANS ENDOCARDITIS

The most apparent symptom in all of the four cases to be reported was the septic type of temperature. The next most outstanding phenomenon was that in three of the four cases another readily demonstrable acute infection preceded the Str. viridans endocarditis.

Anemia was not present in any of the cases. For this reason, probably, percussion revealed no tenderness over the sternum. Extreme clubbing of the fingers was not seen, although in two cases there was slight

clubbing. Janeway's nodes were not present in any case. Petechiae occurred only two or three days before death and were not diffuse—a few were seen in the conjunctivae, some in the mouth and on the hard palate, and some on the chest. Petechiae were not seen in all of the cases.

The cardiac murmur was not as pronounced as in subacute bacterial endocarditis and was more changeable, probably because of the rapidly progressive lesion in the valve and in the mural endocardium. The heart rate was extremely rapid. In one case (case 2) the infection developed on the basis of a fibrillating disease of the mitral valve, which is extremely rare in the subacute cases.

The spleen was large and soft, as in sepsis.

There were no embolic phenomena in the peripheral or the deep blood vessels.

The blood count was not characteristic, although there was a tendency to leukocytosis. Remarkably, despite the severity of the disease, the staff cells were not increased in number. The blood culture in all cases was positive for Str. viridans. According to Hadjopolous,[7] the bacteriologist at Beth Israel Hospital, the type encountered was Str. viridans mites alpha or faecalis, which in his opinion is of greater virulence than the type found in subacute bacterial endocarditis.

In the two cases that came to autopsy the valve was found to be ulcerated. It also showed the presence of very fresh polypous vegetations. In one case, in which the endocarditis was preceded by pneumonia, the polypous deposits were extremely small, the ulceration predominating. In this case there was one infarct in the spleen. In the other case, there were infarcts in the lungs only.

Case 1.—*History.*—A man, aged 20, was admitted to the hospital on March 24, 1932, and died on April 5, 1932. At the time of admission, he had had a temperature of 102 F. and abdominal pain for one week. The pain had diminished, but the temperature continued to be elevated. The pulse rate was 103, and the blood pressure, 120 systolic and 50 diastolic.

The patient had poliomyelitis and scarlet fever in childhood, and acute rheumatic fever at the age of 16. After the attack of scarlet fever, his mother was told that he had valvular disease. However, his recovery was so complete that his uncle, a physician who saw him frequently, said that he was unable to detect any abnormal manifestations in the heart until the onset of the present illness.

Physical Examination.—The heart showed visible apex pulsation in the fifth left interspace, a presystolic thrill over the apex, a presystolic and a systolic murmur over the apex and a loud systolic murmur over the aortic region.

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7. Hadjopolous, L. G., and Burbank, Reginald: Study on Streptococci in Relation to Pathogenicity and Sugar Fermenting Properties, J. Lab. & Clin. Med. **15**:539 (March) 1930.

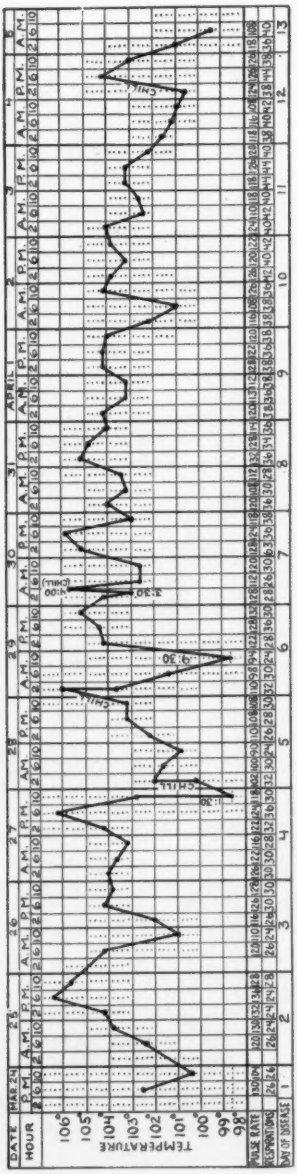

Chart 1.—Temperature chart for case 1.

The spleen was enlarged but not tender.

The liver was much enlarged. The right lobe extended to the umbilicus.

Laboratory Findings.—The electrocardiogram was normal.

The urine showed a faint trace of albumin but otherwise was normal.

The blood count showed: hemoglobin, 54 per cent; red cells, 4,800,000; white cells, 14,700; staff cells, 6 per cent; segmented cells, 33 per cent; polymorphonuclears, 77 per cent; mononuclears, 17 per cent; small lymphocytes, 10 per cent, and monocytes, 7 per cent. The sedimentation rate was 40 per cent.

The blood culture yielded Str. viridans.

Course.—During the patient's entire stay in the hospital, the temperature remained elevated, varying between 100 and 106 F., the rises in temperature always being preceded by repeated chills—a typical septic type of temperature (chart 1). The subjective complaints were headache, occasional vomiting and one nosebleed. Clubbing of the fingers developed during the period in the hospital. Petechiae appeared in the conjunctivae and over the thorax in the last two days of life. On the last day, the patient was icteric. The sensorium was clear to the end.

Comment.—Although we could not trace a recent acute infection in this case, the immediate infection was acute Str. viridans endocarditis of a truly septic type on the basis of a valve that had become chronically diseased as a result of scarlet fever in childhood.

CASE 2.—*History.*—Mrs. E. S., aged 51, was admitted to the hospital on May 29, 1932, and died on June 9, 1932. Seven days before admission she began to suffer from severe headache, fever, nausea, vomiting and general weakness. The temperature was 103 F. Three days later she had a chill after which the temperature rose to 105 F. Just before admission, the temperature rose to 107 F.

Twenty-one years prior to admission the patient noticed precordial pain, after which she experienced frequent attacks of pain in the joints. Thirteen years before she was confined to bed for almost two years, owing to cardiac and articular pains. During the past few years she had been troubled by cystitis and frequent and painful micturition. For the past year and a half she had seen black spots before her eyes. For a long time she had a well compensated mitral stenosis.

Physical Examination.—The patient was lying comfortably in bed, but complained of tenderness over the precordium. There were two pinpoint petechiae without white centers in the left conjunctiva, two small punctate purpuric spots on the right buccal mucous membrane and two punctate petechial spots with white centers in the upper portion of the left side of the chest, anteriorly and posteriorly. The blood pressure was 105 systolic and 65 diastolic.

The heart on percussion was enlarged and fibrillating. The rate was 100. There was a soft blowing murmur over the apex.

Laboratory Findings.—The roentgenogram of the chest was suggestive of mitral stenosis with decompensation. The roentgenogram of the kidneys was normal.

Urine obtained by cystoscopy contained colon bacilli as well as Str. viridans and much pus.

The blood count showed: hemoglobin, 50 per cent; red cells, 3,280,000; white cells, 10,900; staff cells, 23 per cent; segmented cells, 68 per cent; lymphocytes, 6 per cent; monocytes, 2 per cent, and metamyelocytes, 1 per cent. The sedimentation rate was 38 mm. Toxic degeneration of the cells was noted.

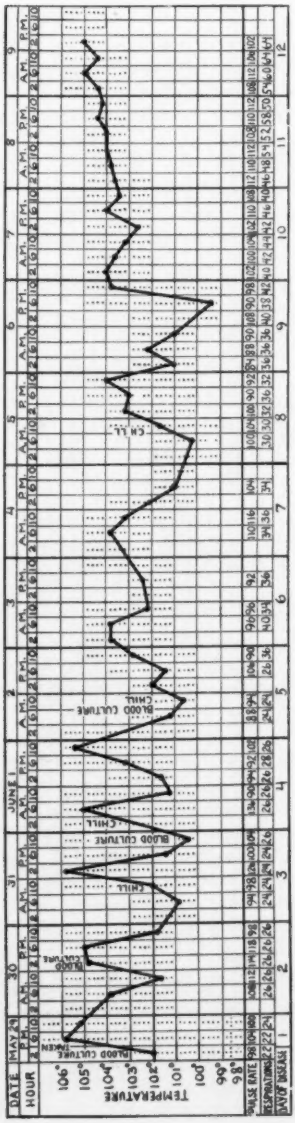

Chart 2.—Temperature chart for case 2.

The first blood culture was sterile; the second showed three colonies of Str. viridans, and the third showed gram-negative bacilli in the broth and one colony of streptococci on the plate.

Course.—Until death, the patient had a septic type of temperature ranging from 101 to 106 F. The urine occasionally showed granular casts, much pus, a few red blood cells, many white blood cells and a four plus reaction to the benzidine test. During the cystoscopic examination, the patient complained of pain in the right costovertebral region. A diagnosis of right pyonephrosis with an obstructed ureter was considered. The trigon showed several submucous hemorrhages and slight trabeculation of the bladder. The patient's mental state was that of confusion and euphoria. She went rapidly downhill, became drowsy and had left facial weakness. The final stages of the illness seemed to indicate cerebral involvement. Fibrillation continued to the end. The spleen was definitelv palpable. The patient died on the twelfth day after admission.

Autopsy (performed by Dr. Alfred Plaut).—The heart weighed 382 Gm. The pericardial sac was intact and contained a small amount of clear fluid. The subepicardial fat was very thick, covering most of the surface. There were no subepicardial hemorrhages. The pulmonary artery was free. The right auricle was considerably wider than is normal and was not hyperemic. The right ventricle was moderately distended. The valves of the right side of the heart were intact. The aortic valve was intact except for slight sclerosis at the base. There was considerable sclerosis of the sinus of Valsalva and of the ascending aorta. The mitral ostium was very narrow. When looked at from above through the very wide left antrum it seemed covered by a smooth ovoid protrusion, which was attached to the mitral valve near the septum. This large vegetation was soft and elastic. Its cut surface was clear and spongy. The valve was shortened. The chordae were short and thick. The atrial surface of the valve was covered with many small protrusions which formed a continuous layer. No lesions were seen in the endocardium of the atrium itself. A wart about 2 mm. high was situated on the tip of the posterior papillary muscle. The left ventricle was narrow, and the myocardium was dark brownish red. Laterally, near the atrioventricular curve, an ochercolored area 3 cm. long was seen on the cut surface. The coronary arteries were moderately sclerotic. The right one was wider than the left.

Both lungs (weight, 990 Gm.) were large, light and emphysematous, with small hyperemic areas in the lower lobes. There was a flat scar in the apex of the left lung, and a small Ghon focus was seen in the lower lobe of the right lung. The arteries of the lungs were slightly arteriosclerotic.

The spleen was slightly enlarged. There were a few capsular thickenings. The organ was soft but not mushy—softer than is usual in subacute bacterial endocarditis and firmer than a septic spleen. It was dark red, and the markings were distinct.

Both kidneys peeled out of the capsule easily. They showed a few small conical abscesses in the cortex. There were no hemorrhages on the surface or on the cut surface. The renal pelves and the ureters were intact. The pelvis of the right kidney showed chronic pyelitis. The bladder was slightly trabeculated. Its mucosa was pale except for the trigon, which was moderately hyperemic. The urethra was very wide.

The results of microscopic examination were as follows: The large vegetation on the mitral valve consisted mainly of micro-organisms and fibrin. The pedicle was edematous and moderately infiltrated with leukocytes and mononuclear elements. The neighboring portion of the endocardium was practically without inflam-

mation. The left coronary artery, which appeared in four sections, was thick-walled, considerably calcified and surrounded by lymphocytic infiltration. The adjoining myocardium appeared normal. Another section from the mitral valve gave the picture of both old and recent endocarditis with much leukocytic infiltration. There were also heaps of bacteria (Str. viridans). There were small areas of calcification at the base of the valve.

The spleen showed much stasis. The centers of the follicles were partly hyalinized. The sclerosis of the vessels was slight. There were some large cells in the pulp, which had basophilic protoplasm and large, irregularly shaped nuclei.

The kidneys presented the classic picture of Löhlein's embolic focal glomerulonephritis. An infarct consisted mostly of necrotic kidney tissue, with the outlines of the tubules and the glomeruli fairly well preserved. Under the capsule and in the axis of the infarct many leukocytes were seen. In the routine slide, no accumulations of micro-organisms were conspicuous. Microscopic serial sections made from the block containing the metastatic renal lesion showed, near the apex of the triangle, a blood vessel which contained thick heaps of micro-organisms. Most of these were morphologically streptococcic. The organisms, however, did not retain the green stain. In some thinner slides colon bacilli also could be made out.

Comment.—This patient had a chronic, well compensated disease of the mitral valve (mitral stenosis and regurgitation). She also had recurrent pyelitis. On this occasion, she took sick with all the symptoms of left-sided pyelonephrosis. No additional signs or symptoms were present to awaken suspicion clinically that a superimposed acute bacterial endocarditis was present. The chills and fever, however, indicated the existence of sepsis, which we thought originally to be due to a focus in the kidney. The catheterized specimen of urine showed both colon bacilli and Str. viridans. Therefore we made a diagnosis of colon bacillus pyelonephrosis and acute Str. viridans endocarditis secondary to the primary infection. The presence of Str. viridans in the urine provided a clue to the diagnosis because it is well known that in Str. viridans endocarditis the organisms may pass through the kidneys with the urine, often so injuring the glomeruli as to cause focal embolic nephritis (Löhlein-Baehr), although they may also pass out with the urine without damaging the kidneys. In the course of an acute infection of an indeterminate nature, if Str. viridans is found in the urine, it provides the clue that the condition is Str. viridans septicemia.

CASE 3.—*History.*—L. G., a man, aged 41, was admitted to the hospital on March 14, 1933, and died on March 20, 1933. On admission, he complained principally of pain in the region of the liver, productive cough, substernal pain, dyspnea, chills and fever (temperature from 101 to 104 F.).

The patient came to the United States twenty-five years prior to admission. He had an attack of rheumatic fever ten years before admission, with swelling of the lower extremities up to the knees, which kept him in bed for six months and out of work for a year. Tonsillectomy was performed during that year. For fifteen years he had had a chronic cough productive of yellowish-white sputum, but no dyspnea or orthopnea was noted. Seven or eight months prior to admission he had an attack of pain radiating to the groin. Roentgen examination gave negative results. His physician stated that two weeks before admission he was icteric.

Eight days prior to admission the patient awoke with a sour taste in the mouth. He was seized with a burning substernal pain and a dull pain across the epigastrium. A druggist relieved the burning pain, but the epigastric pain remained, becoming localized in the right upper quadrant. A severe cough appeared, which was productive of light yellow sputum, never blood-streaked. After prolonged coughing there was slight substernal pain. Since the onset of this illness, the patient had been dyspneic and orthopneic, had had chills and fever (the temperature ranging between 101 and 104 F.) and had noticed that his urine was red.

Physical Examination.—At the time of admission the patient was a dyspneic, orthopneic, cyanotic man, with cardiac decompensation, coughing moderately and expectorating thin, mucopurulent material. The blood pressure was 102 systolic and 65 diastolic.

The pupils were very small and did not react to light or in accommodation. Exophthalmos was present.

The lungs were emphysematous. Numerous rhonchi were noted throughout, and there were many moist râles at the bases, extending rather high and heard in the axillae and anteriorly. There was slight dulness at the bases, with diminished breathing.

The apex of the heart was felt in the fifth interspace in the midclavicular line. A presystolic murmur was heard at the apex. The rate was 100, with regular sinus rhythm; the pulmonary second sound was louder than the aortic second sound.

The liver was felt five fingerbreadths below the costal margin. It was somewhat tender. The spleen was not felt. No ascites was present.

There were clubbing and cyanosis of the finger-tips and toes. A fine tremor was observed in the hands. No edema was present in the extremities.

Laboratory Findings.—A blood count, on March 14, showed: hemoglobin, 71 per cent; red cells, 3,790,000; white cells, 13,000; staff cells, 10 per cent; segmented cells, 70 per cent; polymorphonuclears, 80 per cent, and mononuclears, 20 per cent. The sedimentation rate was 27 mm. The venous pressure was 14 cm.

A blood culture on March 15 was sterile.

A serologic test for syphilis on March 15 gave a doubtful, nonspecific reaction, owing to the presence of pneumonia.

The urine, on March 15, showed: specific gravity, 1.020; an acid reaction; cloudiness; an orange color; no albumin; a few epithelial cells, and some crystals.

The icteric index, on March 15, was 7.

Roentgen examination of the chest, on March 15, gave the following results: There was intense congestion of the lungs. Numerous small patches of bronchopneumonia were diffusely scattered throughout the central portion of the right lung and about the root of the left lung. A small parietal effusion was noted in the lower portion of the right pleural cavity. The shape of the heart was characterized by marked accentuation of the curves of the right auricle and the right ventricle. The curves of the pulmonary artery and the left auricle were not prominent. The diagnosis was bronchopneumonia, purulent effusion, marked cardiac decompensation and mitral disease.

The heart rate, on March 16, was 110 per minute. An electrocardiogram showed: lead II, diphasic T waves, and lead III, negative T waves. It was interpreted as indicating sinus tachycardia with myocardial damage, possibly due to the influence of digitalis.

Course.—March 16: On the day after admission (March 15), the temperature rose to 104.6 F., but it came down to 101.2 F. on March 16. There were numerous rhonchi throughout the chest, with fine crepitant râles at the bases of both lungs. The patient's general condition was poor. He had pain in the rectum as a result of thrombosed hemorrhoids. Phlebotomy was performed, 250 cc. of blood being removed, which caused a slight improvement in the clinical picture. The venous pressure was 18 cm. before phlebotomy and 8 cm. afterward. The diagnosis was bronchopneumonia with cardiac decompensation. Only a systolic murmur was heard at the apex. There were clubbing and cyanosis of the finger-tips.

March 17: Expiratory difficulty was prominent. The temperature fell to 101 F.

March 20: The patient was very ill. Breathing was deep and regular; the respiratory rate was 34, and the pulse was of fair quality, bounding and easily compressible. The lungs were full of moist râles and rhonchi. The patient died.

Autopsy (performed by Dr. Alfred Plaut).—The heart weighed 390 Gm.; it was 11.5 by 10 by 7 cm. and of normal shape. The apex was formed by both ventricles. The subepicardial fat was thick. The mitral ostium was 10.5 cm. wide.

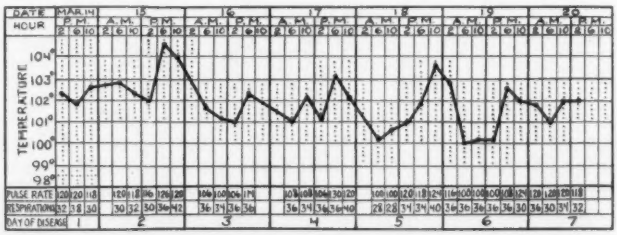

Chart 3.—Temperature chart for case 3.

The left auricle was slightly distended, and the left auricular appendage was narrow. The mitral valve throughout was the seat of old and recent endocarditis. The chordae were attached at the very edge. The webs were gone, but the chordae were only slightly thickened. The edge of the valve was dull, notably near the left edge of the heart. About two thirds of the valvular edge was covered by soft papillary masses which continued upward to the endocardium of the left auricle for nearly 2 cm. above the posterior cusp. The papillary muscles were moderately flattened and hypertrophic. The trabeculae of the left ventricle were more flattened. The left ventricular wall reached a thickness of 1.8 cm. The aortic leaflet was distinctly vascularized; the vessels could be seen with the naked eye up to about 1 cm. from the edge. The posterior leaflet was very short, and no vascularization could be seen in it. In the neighborhood of the auricular endocarditis, small gray, glassy, slightly elevated, round dots were seen in the endocardium. The aortic ostium was 8.5 cm. wide. The posterior cusp was very short. Its edge was rolled toward the wall of the aorta, and it bore a fine row of verrucae. The right cusp was less distorted; the rolling of the edge was conspicuous only in the region of the nodule, and only the posterior half of the cusp was covered with verrucae. The left cusp was slightly posterior. The commissures were drawn out, but only slightly dissociated. The ascending aorta was thin-walled and normal in width and showed much atheroma. The pulmonary ostium and the tricuspid ostium were

normal. The right auricle was slightly wider than normal, and the right auricular appendage was narrow and firm. The right ventricular wall, with trabeculae, reached a thickness of 7 mm. The myocardium was glassy and purplish, with a slight admixture of brown. No scars were seen. The right coronary artery was narrow throughout; the ostium was also narrow and was not surrounded by any scar formation. The left coronary artery was rather wide. The left circumflex branch continued nearly to the right edge of the heart posteriorly.

Both lungs were heavy. There were old adhesions over the upper portion of the upper lobe of the left lung, and some fibrinous layers were present over the whole upper lobe. Both lobes of the left lung were the seat of many confluent bronchopneumonic foci, most of which had completely coalesced. There were interlobar, recent adhesions. The bronchi and the blood vessels showed nothing unusual. There was a shallow scar in the apex. The hilar lymph nodes were anthracotic and soft. The right lung presented a similar picture. In the lower half of the lower lobe the pneumonic foci were more distinctly separated from each other. There was a scar in the right apex.

The thoracic aorta showed little atheroma.

The spleen was large (weight, 300 Gm.; dimensions, 13 by 10 by 5 cm.) and fairly firm. In the capsule, several small, firm, gray thickenings were seen. On the cut surface, numerous irregularly shaped follicles were prominent. The trabeculae were thin. The suprarenal glands were thin.

The left kidney weighed 215 Gm. and was 12.5 by 6 by 3 cm. The right kidney weighed 210 Gm. and was 12 by 6 by 3 cm. The capsules stripped with some difficulty. There were many indistinct, very shallow, purplish depressions, the outlines of which were similar to those of arteriosclerotic scars, although the depressions were much less deep than such scars generally are. The right kidney was the seat of a mixed infarct measuring 2 cm. at the base and 2 cm. in depth. The glomeruli were visible on the cut surface. The striation of the cortex was not very distinct but was normal as far as it was visible. The cortex was slightly wider than is normal. At some spots one had the impression that there might be a mild degree of infarction in small areas. No hemorrhages could be seen.

The results of microscopic examination were as follows:

The liver showed moderate central stasis.

In the kidneys, corresponding to the depressed spots, rather recent scars were seen, most of them showing large round cell infiltration. There were no sclerotic lesions. The glomeruli were cellular throughout, but most of them were intact. At several points characteristic Löhlein lesions were found. In some of them the process seemed to be one of necrosis without embolism.

In the spleen, the germ centers contained much hyalin. The pulp was hyperemic; there were not many leukocytes.

The lungs contained many heart disease cells.

Crush smears from the mitral valve showed cocci of varying sizes and shapes. There were many large involution forms. After treatment of the material with calcium carbonate, culture yielded pure Str. viridans.

The diagnosis was: old and recent mitral and aortic endocarditis with much destruction of the valves; a rheumatic lesion with superimposed bacterial endocarditis; mild dilatation and hypertrophy of the left ventricle; moderate hypertrophy of the right ventricle; swelling of the spleen, with large follicles; a mixed infarct in the right kidney; focal embolic glomerulonephritis (Löhlein); confluent bronchopneumonia of both lungs; scars in the apexes of both lungs; moderate arteriosclerosis of the abdominal aorta and its branches; fatty change in the liver; a small cavernous hemangioma in the right lobe of the liver, and hemorrhoids.

Comment.—Until two weeks before admission to the hospital this patient was well except for an old mitral stenosis. When he was taken ill the condition was correctly diagnosed as bronchopneumonia. During the course of the illness acute Str. viridans endocarditis developed, to which he succumbed within three weeks after the onset of the primary infection.

CASE 4.—*History.*—Mrs. R. W., aged 51, was admitted to the hospital on Nov. 29, 1931, and died on Jan. 11, 1932. On admission her chief complaints were: fever, weakness, prostration, chilly sensations, sweats and anorexia of twelve days' duration and pains on the right side of the head for seven days.

Two weeks before admission the patient began to feel tired, having malaise and a sticking sensation in the left tonsillar region. Two days later she had a temperature of 103 F., was markedly prostrated and complained chiefly of severe aching pains all over the body, especially in the back and the lower extremities. There were marked anorexia and chilly sensations followed by sweats, and the temperature fluctuated for five days between 101 and 105.2 F., being of the septic type. The temperature gradually came down as a result of lysis, but for the five days before admission it was constant between 100 and 103 F. There was marked amelioration of the symptoms so that the patient complained only of weakness, occasional chilly sensations, mild sweats, sharp lancinating pains in the right side of the head, dizziness and anorexia.

The patient had two living children, one aged 26 (with rheumatic cardiac disease) and one aged 23. In childhood she had measles and had her tonsils and adenoids removed. Hysterectomy and bilateral salpingo-oophorectomy were performed three years before for myoma uteri. She had had recurring attacks of left-sided paratonsillitis (two or three attacks yearly) for the past few years. She had occasionally had headaches. Presbyopia had existed for the past few years. Chronic progressive deafness had developed during the past twenty years. There had been no coughing, expectoration, hemoptysis or pain. At an examination for insurance twenty years before, a murmur was heard. There had been no dyspnea, orthopnea or edema. The patient had had marked constipation for many years. She suffered from extreme nervousness and insomnia and cried readily.

Physical Examination.—The patient was a rather pale, thin elderly woman, lying in bed. She was feverish.

The pupils reacted to light and in accommodation. The eyes showed no petechiae or changes in the fundi. The nose showed some scars, left by a previous operation; the mucosa was hypertrophied.

Both ear drums were markedly thickened, and hearing was greatly impaired. The tongue was moist and clean. The teeth were false. The pharynx was impacted. The tonsillar region was inflamed, and some caseous material was present in the right tonsillar fossa.

On examination of the heart, no thrills were felt. The maximum apex impulse was felt at the fifth interspace, in the midclavicular line. There was a short, harsh presystolic murmur at the apex. The pulmonic second sound was accentuated.

The chest, the abdomen and the extremities were normal.

Laboratory Findings.—The urine was normal, except for a faint trace of albumin.

The blood was normal except for slight secondary anemia and a slight increase in staff cells (from 16 to 21 per cent). The sedimentation rate was 31 mm.

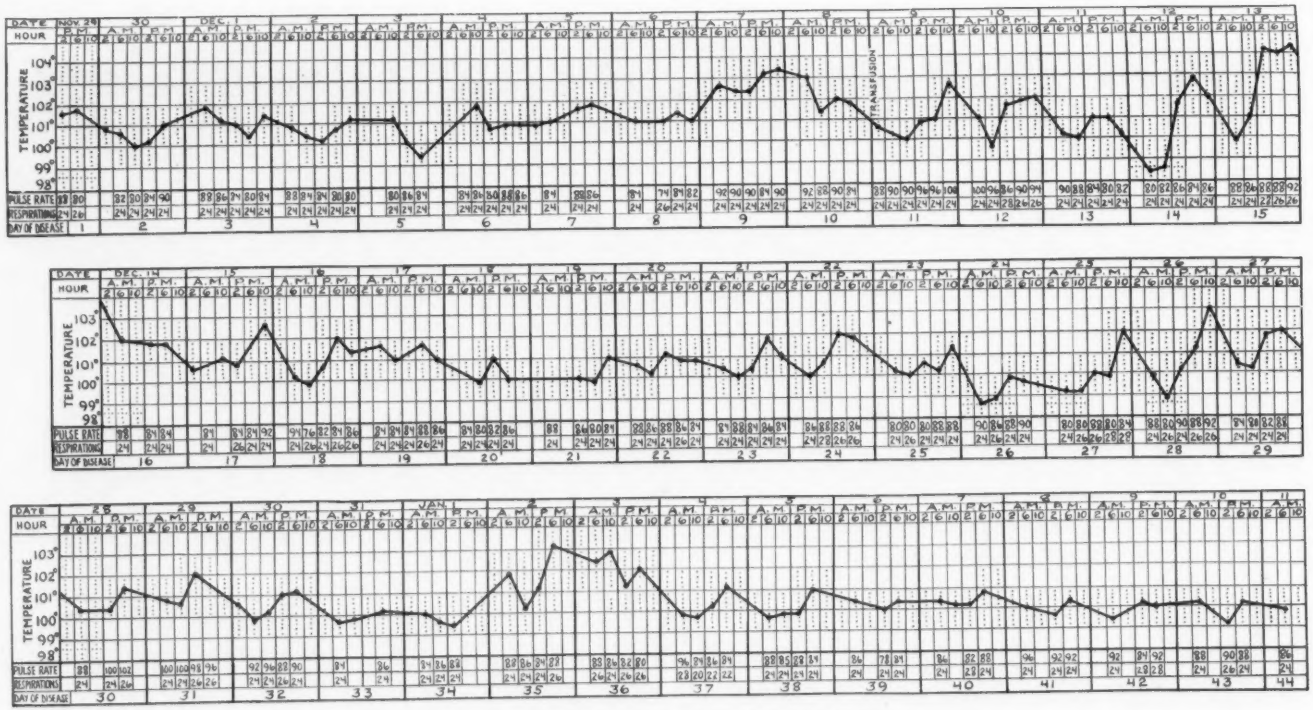

Chart 4.—Temperature chart for case 4.

Blood cultures showed: on Nov. 30, 1931, twenty colonies of Str. viridans; on December 3, sixty-three colonies of Str. viridans mites alpha; on December 10, sixty-six colonies of Str. viridans, and on December 18, Str. viridans.

The results of roentgen examination of the chest, on Nov. 30, 1931, were as follows: The lungs showed moderate emphysema but no infiltration or consolidation. The pleura of the lower lobe of the right lung was thickened. There was calcification of the lymph nodes at the root of the left lung. The heart was not enlarged. The aorta was not sclerotic or dilated.

Course.—The patient was given two transfusions of blood, but went progressively downhill. Toward the end she began to complain of severe pain in the left upper quadrant of the abdomen. She showed typical embolic phenomena in the extremities, and it was necessary to give her narcotics to relieve the pain. On the day of death she began to complain of substernal pain. A mixture of the hydrochlorides of the opium alkaloids was given. Half an hour later she died suddenly.

Comment.—This patient had chronic endocarditis of the mitral valve. She was subject to frequent sore throat, and for several weeks immediately before admission she suffered from a moderately severe sore throat. Since subacute bacterial endocarditis seldom sets in when sore throat is present, it is possible that the sore throat in this case was the expression of a septic tonsillar infection which predisposed the patient to acute fulminating Str. viridans endocarditis.

GENERAL COMMENT

In reviewing the four cases presented, two questions arise: Why is Str. viridans, ordinarily a nonpathogenic organism, pathogenic in certain cases, and why is Str. viridans endocarditis slowly progressive in the majority of cases and rapidly fatal in a few?

As a rule, the effect of a micro-organism depends on its virulence as well as on the resistance of the body, i. e., the existing immunity. The theory that under certain conditions a nonpathogenic organism can suddenly, by mutation, become virulent does not seem entirely plausible. It seems far more reasonable to assume that the increased virulence of an organism is due to the fact that some pathologic process has offered it a more favorable culture medium. That Str. viridans becomes virulent in this way is shown, we believe, not only by the fact that it can become pathogenic in a previously diseased endocardium but by the fact that it can become pathogenic when implanting itself in chronically diseased bile ducts, causing cholangeitis lenta.

As to the factors that determine whether Str. viridans endocarditis will be rapidly fatal or slowly progressive, it is well known that in addition to lowered general immunity alteration in tissue immunity is important. A disturbance in local tissue reaction determines, in the first place, the possibility of cohesion between invading bacteria and the tissue. In bacteremia, although bacteria must necessarily pass through the cardiac

valves and the heart, bacterial invasion of normal valves or a normal heart is a great exception. Even in cases of severe sepsis in which multiple abscesses are found in the heart, the valves remain intact. Orth [8] demonstrated this experimentally, as he was able to produce bacterial endocarditis by injecting bacteria intravenously only in rabbits in which the endocardium had been previously damaged.

When cohesion is possible, owing to loss of tissue reaction, the progress of the local pathologic change depends largely on the reactivity of the reticulo-endothelium. Whenever there is bacterial invasion of the blood, the main factor in the defense mechanism is the reticulo-endothelium of the liver, the spleen and the bone marrow, which first destroys and then absorbs the end-products of the micro-organisms without permitting damage to the parenchyma of the organs. This explains why, in the course of most infections, the liver and spleen are practically unaffected, except, possibly, for enlargement and softening of the spleen. The function of the reticulo-endothelium of the bone marrow, when there is bacterial invasion, is not only to destroy the invaders but to stimulate the leukoblastic apparatus so that in most cases leukocytosis with polymorphonucleosis develops, and occasionally also a considerable increase in immature white cells (staff cells).

Lexer [9] recently furnished an explanation of why the reticulo-endothelium in the liver, spleen and bone marrow is so effective in absorbing the end-products of bacteria. By injecting a solution of india ink intravenously into rabbits, he was able to show that absorption is most rapid and most complete where the lumens of the capillaries are largest, namely, in the liver, the spleen and the bone marrow. Where the capillaries are of medium size, as in the kidneys and the lungs, absorption is not so rapid, and where they are smallest, as in the skin, absorption is almost negligible.

If the reactive power of the reticulo-endothelium is abnormally low, either because of its own deficiency or because of an overwhelming bacterial invasion, not only do the small and medium capillaries fail to react properly, but even the largest capillaries in the liver, spleen and bone marrow fail similarly. The result is multiple suppurative areas in the liver and even in the spleen; the loss of reactive function of the reticulo-endothelium of the bone marrow manifests itself as a disturbance in the leukoblastic element, so that there is marked reduction in the granulocytes, resulting in subgranulocythemia or possibly agranulo-

8. Orth, J.: Ueber die Aetiologie der experimentellen mycotischen Endocarditis, Virchows Arch. f. path. Anat. **103**:333, 1886.

9. Lexer, E.: Die autoplastische Deckung von Schädellücken aus dem Beckenkamm, Deutsche Ztschr. f. Chir. **239**:743 (Jan. 1) 1933.

cythemia. In the still more severe cases, erythropoiesis is likewise interfered with so that marked secondary anemia occurs. Occasionally the megakaryocytic activity also is disturbed, bringing about thrombocytopenia with hemorrhagic diathesis.

In cases of severe bacterial invasion, the reactive power of the reticulo-endothelium may be more disturbed in other parts of the body than in the liver, spleen and bone marrow, so that one finds thrombi in all of the middle-sized and small capillaries throughout the body, even in the skin. In some cases, the capillaries or the superficial arterioles of the skin become so blocked with thrombi as to cause large areas of cutaneous necrosis. When the condition continues for several days, the tissues supplied by the blood vessels undergo suppuration and necrosis, so that the smaller arterioles and capillaries may become soft and break; this explains multiple diffuse hemorrhage in severe cases of sepsis. In these cases, it is not arteritis or capillaritis which causes an obstruction to the flow of blood to the surrounding tissues, but actual blockage by thrombi that are the result of bacterial action on the walls of the vessels.

Siegmund [10] and Dietrich,[11] on the basis of experimental and pathologic studies, classified the reactive power of the reticulo-endothelium to invading micro-organisms into three grades: (1) areactive, in which there is absolute loss of this power; (2) partially reactive, in which the function of the reticulo-endothelium is incomplete, and (3) reactive, in which the response is so favorable that the invaders are destroyed and their end-products absorbed.

It is important to keep in mind that the reaction of the reticulo-endothelium to bacterial invasion is not alike throughout the body. Only in the severest types of infection is the entire reticulo-endothelium reactive. In the vast majority of cases, the reticulo-endothelium is reactive in some parts, as in the liver, spleen and bone marrow, but partially reactive or areactive elsewhere. This would explain why in many cases cohesion between the invading micro-organisms and the tissue takes place only in certain parts of the body, giving rise to localized pathologic changes. If cohesion between bacteria and tissue is not to take place in any part of the body, there must be a generally reactive response of

10. Siegmund, H.: Untersuchungen über Immunität und Entzündung, Verhandl. d. deutsch. path. Gesellsch. **19**:114, 1923; Gefässveränderungen bei chronischer Streptokokkensepsis, Centralbl. f. allg. Path. u. path. Anat. **35**:276, 124; Zur Pathologie der chronischen Streptokokkensepsis, München. med. Wchnschr. **72**: 639, 1925.

11. Dietrich, A.: Die Reaktionsfähigkeit des Körpers bei septischen Erkrankungen in ihren pathologisch-anatomischen Aeusserungen, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **37**:180, 1925.

the reticulo-endothelium of the entire body. In other words, the reactive reticulo-endothelium kills the bacteria and absorbs the end-products so completely as to allow no pathologic changes, or at most extremely insignificant changes. These mild changes may be inflammatory and lead eventually to healing. This is exemplified by those cases of acute general infection in which, although there are physical signs pointing to endocardial involvement, if the patient succumbs to the general infection the endocardium shows but slight inflammatory change. If the patient recovers, all endocardial signs disappear, as a rule, owing to complete healing. In some cases, of course, during the process of healing the inflammatory changes cause some deformity of the valve, as illustrated by chronic rheumatic or syphilitic valvular disease.

When there is only a partially reactive reticulo-endothelium, there is but partial interference with the destructive process of the bacteria. In subacute bacterial endocarditis, the reticulo-endothelium is only partially reactive; hence the inflammatory changes (polypous excrescences) in the endocardium. In many of these cases the reactive power of the reticulo-endothelium might still be sufficient to withstand the invasion and permit of recovery of the patient were it not for the location of the lesion. The location is not only one where the lesion is irremovable but one from which emboli can be carried readily through the blood stream to the most distant parts of the body to cause death. In other words, it is the consequences of this polypous type of bacterial endocarditis, in which the excrescences serve as a continuous focus of infection, that bring about the fatal termination.

In acute Str. viridans endocarditis, on the other hand, the reticulo-endothelium of the endocardium is no longer partially reactive but is areactive; in three of our four cases, this was the result of a severe, immediately preceding infection. The areactive reticulo-endothelium of the endocardium furnishes an exceedingly good culture medium for the invading micro-organism, so that the now very virulent Str. viridans can carry on its damaging activity with great rapidity, producing ulcerated areas on the endocardium and endocardial sepsis that runs quickly to a fatal conclusion.

CONCLUSIONS

1. Str. viridans may be the cause of acute, rapidly fatal endocarditis occurring on the basis of a previously diseased valve.

2. This form of endocarditis is usually preceded by some previous acute infection of several days', or at the most several weeks', duration. This was so in three of the four cases reported here. As the primary infection precedes the acute endocarditis by only a few days, it may so efface the symptoms of endocarditis as to make the diagnosis of acute

Str. viridans endocarditis impossible ante mortem, as in the case in which the condition was preceded by pneumonia. In all our cases, the symptoms of septicemia were in the foreground.

3. We believe that the reason why the cases reported had a rapidly fatal, instead of a protracted fatal, course, is that there was almost total loss of the reactive power of the reticulo-endothelium of the endocardium. A primary factor in the areactive quality of the reticulo-endothelium was an immediately preceding acute infection. Because the reticulo-endothelium of the endocardium was areactive, local inflammatory changes were minor and destructive changes maximal.

STUDIES OF THE BLOOD IN NORMAL PREGNANCY

V. CONDUCTIVITY, TOTAL BASE, CHLORIDE AND ACID-BASE EQUILIBRIUM

WILLIAM J. DIECKMANN, M.D.
CHICAGO
AND
CARL R. WEGNER, M.D.
ST. LOUIS

Studies of the acid-base equilibrium of the plasma in pregnancy have been incomplete either because they were based on too few patients or because all of the various cations (sodium, potassium, calcium, magnesium or total base) and anions (Cl^-, HCO_3^-, HPO_4^-, SO_4^-, protein and organic acid) were not determined. Stander and his co-workers made a complete study of the acid-base equilibrium in three pregnant women. Oard and Peters made a similar study in twelve pregnant women, but omitted determinations of SO_4^- and organic acid. Numerous other reports of studies of the carbon dioxide content and, in a few instances, of p_H have been published, but the number of reports of total base in pregnancy is extremely small. However, similar reports on nonpregnant persons are also few and are based on a study of a relatively small number of subjects.

In table 1 are listed some of the published data for these various substances in nonpregnant and pregnant women. The average figure is given for the nonpregnant group. None of the investigators, so far as we know, have obtained their data from the same women for the different periods of pregnancy; therefore, the lowest average figure is given. In view of the marked changes in some of these substances associated with pregnancy and the inability of any one to explain the mechanism involved, the number of reports is surprisingly small.

The range for determined total base in the normal subject is from 147 to 161 millimols, with an average of 154, while in pregnancy the range is from 139 to 158 millimols, with an average of 147.

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From the Department of Obstetrics and Gynecology, Washington University School of Medicine, the St. Louis Maternity Hospital, the Department of Obstetrics and Gynecology, University of Chicago, and the Chicago Lying-in Hospital and Dispensary.

TABLE 1.—*Reported Averages for Total Base, Conductivity, Carbon Dioxide Content, p_H and Serum Chlorides in Nonpregnant and Pregnant Persons*

	Number of Subjects	Total Base, mM.*	Conductivity as Sodium Chloride,† Per Cent	Conductivity as Sodium Chloride,† mM.*	Serum Sodium Chloride, mM.*	Carbon Dioxide, per Cent by Vol.	p_H
Nonpregnant							
Kramer and Tisdall..... (J. Biol. Chem. **53**: 241, 1922)	10	158.0‡	.....	.....	.....	....	....
Briggs ..... (J. Biol. Chem. **57**: 351, 1923)	2	153.6‡	.....	.....	102.5	....	....
Salvesen and Linder..... (J. Biol. Chem. **58**: 617, 1924)	7	153.3‡	.....	.....	.....	....	....
Salvesen ..... (Acta med. Scandinav. **69**: 126, 1928)	6 F§	151.0	.....	.....	106.2	59.0	7.47
Kydd, Oard and Peters..... (J. Biol. Chem. **98**: 241, 1932)	8 F	153.8	.....	.....	.....	61.6	7.39
Peters et al. ..... (J. Biol. Chem. **67**: 141, 1926)	15	155.7	.....	.....	103.5	57.8	....
Stander et al. ..... (J. Biol. Chem. **85**: 233, 1929)	3 F	155.3	.....	.....	106.6	56.9	7.34
Atchley and Benedict..... (J. Clin. Investigation **9**: 265, 1930)	10	151.9	.....	.....	103.5	65.0	....
Sunderman et al. ..... (J. Clin. Investigation **3**: 37, 1926)	8	154.7	.....	133.0	104.0	....	....
Darrow and Hartmann..... (Am. J. Dis. Child. **37**: 51, 1929)	13	150.7	.....	.....	100.0	55.3	....
Gram and Cullen..... (J. Biol. Chem. **57**: 477, 1923)	..	.....	0.799	136.7	103.3	....	....
Earle and Cullen..... (J. Biol. Chem. **83**: 545, 1929)	78 F	.....	.....	.....	.....	64.0	7.45
Siedentopf and Eissner..... (Ztschr. f. Geburtsh u. Gynäk. **97**: 17, 1930)	23	.....	.....	.....	.....	....	7.37-7.40
Wirz ..... (Arch. f. Gynäk. **139**: 511, 1930)	16	.....	.....	.....	.....	....	7.46
Range		147-161	0.787-0.810		97-110	49-74	7.33-7.51
Average		154.0	0.799	134.8	103.7	64.0	7.4
Pregnant							
Michaelis, L. ..... (Die Wasserstoffionen-Konzentration, Berlin, Julius Springer, 1914)	23	.....	.....	.....	.....	....	Alkaline
Hasselbach and Gammeltoft..... (Biochem. Ztschr. **68**: 206, 1915)	8	.....	.....	.....	.....	....	Normal
Bock ..... (Arch. f. Gynäk. **131**: 468, 1928)	15	.....	.....	.....	.....	....	Acid
Krebs and Briggs..... (Am. J. Obst. & Gynec. **5**: 67, 1923)	17	145.9‡	.....	.....	99.9	....	....
Marrack and Boone..... (Brit. J. Exper. Path. **4**: 261, 1923)	17	144.5‡	.....	.....	100.9	53.8	....
Dennis and King..... (Am. J. Obst. & Gynec. **7**: 233, 1924)	16	159.5‡	.....	.....	96.9	48.8	....
Stander et al.[2].....	3	147.0	.....	.....	104.1	46.3	7.37
Kydd, Oard and Peters..... (J. Biol. Chem. **98**: 241, 1932)	10	145.8	.....	.....	103.7	52.6	7.36
Gaebler and Rosene..... (Am. J. Obst. & Gynec. **15**: 808, 1928)	32	.....	.....	.....	.....	48.0	....
Siedentopf and Eissner..... (Ztschr. f. Geburtsh. u. Gynäk. **97**: 17, 1930)	95	.....	.....	.....	.....	....	7.45
Wirz ..... (Arch. f. Gynäk. **139**: 511, 1930)	30	.....	.....	.....	.....	....	7.49
Range		139-158	.....	.....	90-107	38-61	7.28-7.46
Average		147	.....	.....	101 (590 mg.%)	50.0	7.4

* mM. indicates milliequivalents per liter.
† The results are corrected for the depression of conductivity caused by serum protein.
‡ The sum of individual determinations of cations.
§ F indicates female subjects.

Chlorides in the normal subject range from 97 to 110 millimols, with an average of 103.7, while in pregnancy the range is from 90 to 107 millimols, with an average of 101.

The reports of the alkali reserve have been given both as carbon dioxide content and as bicarbonate. The normal carbon dioxide content of the blood ranges from 49 to 74, with an average of 64 per cent by volume, while in pregnancy the range is from 38 to 61, with an average of 50 per cent by volume. The figures for bicarbonate are usually about 3 per cent by volume lower. The alveolar and arterial carbon dioxide tensions in the normal resting person vary from 37 to 58, with an average of 40, while in pregnancy the average is 33 mm. of mercury.

A study of the reports of p_H in pregnancy seems to indicate that the change, if any, is toward the alkaline side. In a recent journal Kydd and his co-workers, basing their opinion on reports in the literature, especially on that of Stander (three determinations) and on their own study of ten pregnant women, stated that there is no change in p_H. Myers and his co-workers,[1] also basing their opinion on reports in the literature, especially on those of Gaebler and Rosene (fifty-six observations on thirty-two pregnant women), Siedentopf and Eissner (ninety-five observations on ninety-five pregnant women), and Wirz (thirty pregnant women), stated that the p_H is definitely increased toward the alkaline side. This citing of authorities by these two groups of investigators, with different interpretations, indicates a lack of study of the reported data by both. Thus, Gaebler and Rosene studied patients only during the last two months of pregnancy. Siedentopf had ninety-five observations on different women for the ten lunar months, thus including from one to twenty-eight patients in each group, and his conclusion is that the p_H is increased toward the alkaline side. However, if we divided his figures into three consecutive groups, which are large enough for statistical analysis, we find no change of any significance. It seems evident to us that these various investigators have disregarded the wide range of p_H found in normal persons as well as the hourly variations and have ascribed undue significance to the slight change found in pregnancy. Earle and Cullen stated that hourly determinations indicate that there are marked fluctuations of p_H, but that there is a general tendency for it to increase during the day. This increase ranges from p_H 0.01 to 0.07, the latter figure of which is greater than the reported increase in pregnancy. This controversy can be settled only by serial determinations of the carbon dioxide content and p_H in at least twenty women who are studied at frequent intervals during pregnancy.

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1. Myers, V. C.; Muntwyler, E., and Bill, A. H.: Acid-Base Balance Disturbance of Pregnancy, J. Biol. Chem. **98**:253 (Oct.) 1932: Alleged Alkalosis in Pregnancy, ibid. **98**:267 (Oct.) 1932.

Serial studies of these various constituents were made by us on the same women during pregnancy and the puerperium to determine the change in the individual case. Figures for plasma volume, obtained with congo red, as described in previous articles, were available. Thus the total amounts of base and combined electrolyte (conductivity) could be calculated and the direction and degree of change determined.

METHOD

Blood was obtained in oiled syringes without stasis. A portion was injected under oil into centrifuge tubes. The clot was separated in all cases in from twenty to forty minutes, and after centrifugation the serum was removed and kept under oil. All determinations were made on this serum. For total base determinations, the Stadie-Ross method was used, but the proteins were first removed by precipitation with heat and acetic acid in a bomb, because digestion and ashing could then be carried out with less loss of base due to sputtering or creeping. Determinations of carbon dioxide content were made with the Van Slyke constant volume apparatus, using 1 cc. of serum. Determinations of p_H were made with the Hasting-Sendroy bicolorimetric method. Chlorides were determined with the Wilson-Ball modification of Van Slyke's method. The wheatstone-bridge of the Leed and Northrop student potentiometer, a microphone hummer as a source of high frequency current, a resistance box and earphones were used for the determination of the conductivity. The cell was a special one made by Leed and Northrop, requiring approximately 2 cc. of serum, and could be sealed to prevent loss of carbon dioxide. All readings were made at 20 C. The instrument was calibrated with known solutions of sodium chloride and was checked on numerous occasions. The average of a number of readings was always taken, and we believe that this measurement of serum electrolytes is far more exact than the determinations of total base. Corrections were made, the Gram formula for the depression caused by the proteins being used.

$$C_c = \frac{C_o \times 100}{100 - (d \times p)}$$

C_o = observed conductivity (as percentage of sodium chloride)

C_c = corrected

p = serum protein

d = 2.2, Gram's factor for depression caused by 1 per cent protein

Conversion of the percentage of sodium chloride to millimols and the multiplication of the latter figure by the factor, 1.16, gives a value which is essentially equal to the total base. As has been stated, the patients designated as series A, were followed throughout pregnancy and the puerperium. Another group, series B, was studied from term to eight weeks post partum, and the total group is composed of the fore-

going and many for whom single determinations were made. Plasma volumes were determined in all cases, and the multiplication of the volume by any of the substances determined gave the total amount of this substance in the circulation. We admit that we cannot determine the true plasma volume, but we believe, and have advanced proof in previous articles, that consistent results can be obtained. Since all determinations were made by one person, with a carefully controlled technic, we believed that variations in the total amounts are of significance.

In table 2 is listed the conductivity, expressed as percentage of sodium chloride, for the different periods. The average for the normal

TABLE 2.—*Conductivity of the Serum in Percentage of Sodium Chloride: Variations and Averages in Pregnancy and the Puerperium*

	Number of Patients							
	Ante Partum, Weeks				Post Partum, Days			
Percentage	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 15	18 to 26	8 to 17 Weeks
0.740-0.749	..	..	1	4	..	..	..	..
0.750-0.759	2	..	..	5	2	..	..	..
0.760-0.769	2	2	3	12	6	3	1	..
0.770-0.779	5	2	8	12	3	10	3	..
0.780-0.789	10	3	5	14	8	9	4	4
0.790-0.799	3	1	4	4	4	5	..	1
0.800-0.810	1	2	3	1	1	1	1	4
Total	23	10	24	52	24	28	9	9
	Means							
Total cases	0.780 ± 0.002	.....	0.780 ± 0.002	0.773 ± 0.001	0.791 ± 0.002	0.782 ± 0.001		
Standard deviation	0.012	.....	0.015	0.014	0.014	0.01		
Series A	0.780	0.786	0.782	0.771	0.776	0.775		
Series B	.....	.....	.....	0.771	0.774	0.780	0.790	0.795

Normal range: 0.787-0.810 per cent; 134.5-138.4 millimols

nonpregnant person is 0.800 per cent. It is evident that there is a definite decrease of the total electrolytes in pregnancy, reaching a minimum of 0.771 per cent at term, and that it requires at least from six to eight weeks after delivery before the conductivity is again normal. Statistical calculations indicate that the mean at term, compared with the normal mean and also with the mean for from ten to fifteen days post partum, demonstrates that the changes are of significance. This decrease in conductivity, meaning a decrease in the total electrolyte (serum ash), is at variance with the statement made by Stander and Tyler [2] that the plasma ash remains normal during pregnancy. Their failure to detect significant changes is due to the fact that the method used by them is not sufficiently sensitive.

2. Stander, H. J., and Tyler, M.: Moisture and Ash of Maternal and Foetal Blood, Surg., Gynec. & Obst. **31**:276 (Sept.) 1920.

In table 3 are listed the conductivities expressed as grams of sodium chloride per kilogram of body weight. These figures were obtained by multiplying the plasma volume by the percentage of sodium chloride and

TABLE 3.—*Conductivity of the Serum as Grams of Sodium Chloride per Kilogram of Body Weight: Variations and Averages in Pregnancy and the Puerperium*

	Number of Patients							
	Ante Partum, Weeks				Post Partum, Days			
Gm. per Kg.	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 15	18 to 26	8 to 17 Weeks
0.25-0.29	4	1	2	5	..	1	..	..
0.30-0.34	5	1	5	7	7	8	2	1
0.35-0.39	7	3	10	17	6	10	1	5
0.40-0.44	4	4	4	16	7	2	2	3
0.45-0.49	3	1	1	5	4	4	2	..
0.50-0.54	..	..	1	2	..	3	2	..
Total	23	10	23	52	24	28	9	9
	Means							
Total cases	0.364 ± 0.009	.....	0.37 ± 0.008	0.384 ± 0.006	0.387 ± 0.006	0.386 ± 0.009		
Standard deviation	0.067	.....	0.057	0.061	0.057	0.070		
Series A	0.34	0.38	0.36	0.36	0.36	0.40		
Series B	....	....	....	0.39	0.36	0.39	0.44	0.38

TABLE 4.—*Total Base, Millimols: Variations and Averages in Pregnancy and the Puerperium*

	Number of Patients							
	Ante Partum, Weeks				Post Partum, Days			
Millimols	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 15	18 to 26	8 to 17 Weeks
140-144	2	1	..	9	1	4	1	..
145-149	1	3	6	8	4	3	1	2
150-154	6	4	11	14	5	5	1	1
155-159	9	..	5	8	4	11	4	2
160-164	2	..	1	3	1	4	1	1
165-170	1	..	..	..	1	..	..	2
Total	21	8	23	42	16	27	8	8
	Means							
Total cases	154.6 ± 0.8	.....	152.2 ± 0.6	150.6 ± 0.6	152.9 ± 1.0	153.5 ± 0.8		
Standard deviation	5.9	.....	4.1	6.0	6.2	6.4		
Series A	156	.....	150	152	154	151		
Series B	...	.....	...	148	152	162	...	158

Normal range: 147-161 millimols

dividing the product by the body weight. These data demonstrate that the total electrolyte in pregnancy, if calculated on a weight basis, shows no significant change.

In table 4 are listed the data for total base. The range is wide, but the relatively small standard deviations indicate that the majority of the figures fall between 145 and 160. The decrease at term is significant. Oard and Peters, in an attempt to account for this decrease, which they

stated amounts to approximately 8 millimols, ascribed 3 millimols to the decrease in serum protein, citing the work of Plass and his co-workers as proof of the lowered proteins. However, serial determinations of serum protein in pregnancy indicate a reduction which will account for approximately from 0.5 to 1.5 millimols, instead of the 3 millimols postulated by them. In a previous article [3] we have indicated certain errors in the work of Plass and his co-workers and have also demonstrated that the change in serum protein in pregnancy is not as great as heretofore reported. Furthermore, Oard and Peters' conclusions are based on twelve determinations, which is too small a number for any consideration. There is a definite decrease in total base, amounting to from 4 to 6 millimols, which probably can be accounted for in part by the decrease in protein and bicarbonate, but a portion is unaccounted

TABLE 5.—*Average Changes in Conductivity (as Sodium Chloride) and Total Base, Calculated on Total Amount Variations, Using the Initial Determination as One Hundred Per Cent for the Antepartum Period*

	Conductivity		Total Base	
	No. of Cases	Change, per Cent	No. of Cases	Change, per Cent
From 26 to 35 weeks of gestation				
Average increase for all patients	16	16.8	15	18.0
Average increase for those showing increase	10	30.4	11	26.1
Average decrease for those showing decrease	4	21.3	2	9.5
No change	2	0	2	0
From 36 to 40 weeks of gestation				
Average increase for all patients	14	22.7	12	20.6
Average increase for those showing increase	10	32.4	12	20.6
Average decrease for those showing decrease	1	7.0	0	0
No change	3	0	0	0

for, and it is most important that no satisfactory explanation has been given for any of these changes.

In table 5 are listed the average changes in variations in the total amount of the conductivity and total base. These figures were obtained by the following calculations: The plasma volume is multiplied by the conductivity or total base, and the product is the total amount. The first determination is then assumed to be 100 per cent, and all subsequent readings are divided by this one, thus converting all figures to percentage of increase or decrease, making it possible to compare changes in different persons. At thirty weeks' gestation the majority of the patients had an increase of 17 per cent both in conductivity and in total base. At term all of the patients, with but one exception, showed an increase of 21 per cent in total base. The average increase in the conductivity was 23 per cent, with only one patient showing a decrease. It is evident that there is a definite increase in the total amount of both the anions

3. Dieckmann, W. J., and Wegner, C. R.: Studies of the Blood in Normal Pregnancy: IV. Percentages and Grams per Kilogram of Serum Protein and Fibrin and Variations in Total Amount of Each, Arch. Int. Med., to be published.

and the cations of the plasma in pregnancy. This is due, of course, to the increase in plasma volume and the necessity of maintaining osmotic equilibrium.

In table 6 are listed the changes in conductivity and total base, calculated on the total amount for the puerperium. The determination

TABLE 6.—*Average Changes in Conductivity (as Sodium Chloride) and Total Base, Calculated on Total Amount Variations, Using the Last Antepartum Determination as One Hundred Per Cent for the Postpartum Period*

	Conductivity		Total Base	
	No. of Cases	Change, per Cent	No. of Cases	Change, per Cent
From 2 to 6 days post partum				
Average decrease for all patients	23	8.9	14	14.0
Average decrease for those showing decrease	12	19.5	10	20.0
Average increase for those showing increase	2	16.0	1	7.0
No change	9	0	3	0
From 10 to 25 days post partum				
Average decrease for all patients	33	5.7	28	1.4
Average decrease for those showing decrease	22	15.2	15	14.5
Average increase for those showing increase	6	23.2	5	21.0
No change	5	0	8	0
From 8 to 17 weeks post partum				
Average decrease for all patients	9	13.2	5	8.0
Average decrease for those showing decrease	8	15.5	3	12.7
Average increase for those showing increase	1	6.0	0	0
No change	0	0	2	0

TABLE 7.—*Carbon Dioxide Content, Per Cent by Volume per Hundred Cubic Centimeters of Serum: Variations and Averages in Pregnancy and the Puerperium*

	Number of Patients							
	Ante Partum, Weeks				Post Partum, Days			
Per Cent by Volume per 100 Cc. of Serum	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 15	18 to 26	8 to 17 Weeks
40-44	..	..	..	3	..	1	..	..
45-49	1	1	2	7	3	1	..	..
50-54	5	3	3	9	4	5	1	1
55-59	4	3	6	22	10	16	6	..
60-64	..	..	..	1	2	1	..	..
Total	10	7	11	42	19	24	7	1
			Means					
Total cases	53	53	54	53	54	55	55	50
Series A	54	..	55	53	58	54		
Series B	.	..	..	52	54	54		

Normal range: 49-75 per cent by volume

at term was assumed to be 100 per cent, which was used as the divisor. The majority of the patients showed decreases in the total amount of plasma electrolyte after delivery, but the decrease was not as great as the increase during pregnancy. The probable explanation lies in the fact that many of these patients weighed more after delivery, thus requiring a larger volume of plasma, and the concentration of these substances increased as they returned to normal.

In table 7 are listed the variations and averages for the carbon dioxide content. Unfortunately, while the number of determinations

is large, few patients were followed thoroughout pregnancy. The figures for the averages at the different periods show little variation, thus again demonstrating the fallacy of studying groups rather than the same subjects at different times. It is evident from the determination of the carbon dioxide content that no marked acidosis exists in pregnancy.

TABLE 8.—*Variations and Averages of p_H in Pregnancy and the Puerperium*

	Number of Patients						
	Ante Partum, Weeks				Post Partum, Days		
p_H	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 15	18 to 26
7.30-7.34	..	..	..	..	..	..	2
7.35-7.39	3	2	3	14	4	7	..
7.40-7.44	6	2	4	18	7	12	4
7.45-7.47	..	..	..	1	1	..	..
Total	9	4	7	33	12	19	6
	Means						
Total cases	7.40	7.39	7.39	7.39	7.39	7.39	7.37
Series A	7.40	....	7.39	7.38			
Series B	....	....	....	7.40	7.39	7.39	

TABLE 9.—*Sodium Chloride Milligrams per Hundred Cubic Centimeters: Variations and Averages in Pregnancy and the Puerperium*

	Number of Patients							
	Ante Partum, Weeks				Post Partum, Days			
Mg. per 100 Cc.	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 15	18 to 26	8 to 17 Weeks
560-579	2	..	1	5	4	..	2	1
580-589	1	..	1	3	1	3	2	2
590-599	7	3	2	14	9	6	4	1
600-609	2	2	8	5	5	5	1	..
610-619	12	4	9	16	6	17	..	3
620-639	..	2	3	11	..	2	..	3
Total	24	11	24	54	25	33	9	10
	Means							
Total cases	603.3 ± 1.8	.....	607.3 ± 1.6	605.1 ± 1.5	597.3 ± 1.7	607.2 ± 1.3		
Standard deviation	13.0	.....	11.8	15.7	12.8	11.1		
Series A	604	605	609	612	595	602		
Series B	...	...	...	596	594	612	593	606

Normal range: 567-643 mg. per 100 cc.; 97-110 millimols

In table 8 are listed the variations and averages for the p_H. Too few patients were followed throughout pregnancy, but the large number of determinations, all within normal limits, demonstrate definitely that no acidosis exists. The normal p_H, together with the decrease in carbon dioxide content and bicarbonate, indicates that a condition of compensated alkali or carbon dioxide deficit exists. It is most unfortunate that more determinations of p_H were not made in series A, because only serial observations can settle definitely the controversy as to

TABLE 10.—*Data on Patients Followed Throughout Pregnancy and the Puerperium (Series A)*

Patient, Gravida, Color,* Age	Period of Gestation or Post Partum	Conductivity as Sodium Chloride: Per Cent	Gm. per Kg.	Change, per Cent	Plasma Volume Change, per Cent	Total Base: Change, per Cent	mM.†	Sodium Chloride, Mg. per 100 Cc.	Carbon Dioxide, per Cent by Vol.	p_H
1	13 wks.	0.792	0.32	...	...	...	158	619	..	....
II	29 wks.	0.794	0.44	167	166	159	151	603	..	....
W	40 wks.	0.746	0.48	194	206	197	151	...	..	7.37
20	12 days	0.776	0.54	94	90	93	156	607	..	7.40
2	14 wks.	0.792	0.30	...	...	...	158	619	..	....
I	30 wks.	0.794	0.33	115	115	105	145	619	..	....
W	40 wks.	0.783	0.34	117	119	116	154	625	50	....
23	12 days	0.783	0.32	87	86	81	143	619	58	....
3	15 wks.	0.781	0.44	...	...	...	159	590	..	....
I	30 wks.	0.768	0.47	123	125	116	147	603	..	....
W	40 wks.	0.775	0.42	115	116	115	158	613	..	....
25	12 days	0.783	0.46	92	91	89	155	601	..	....
4	14 wks.	0.782	0.25	...	...	...	153	619	..	....
VII	27 wks.	0.783	0.31	122	122	122	153	603	..	....
W	40 wks.	0.752	0.35	128	133	...	...	619	..	....
30	14 days	0.768	0.28	76	75	84	157	586	..	....
5	12 wks.	0.780	0.31	...	...	...	155	613	..	....
II	28 wks.	0.774	0.36	128	129	125	150	603	..	....
W	39 wks.	0.764	0.38	137	140	136	151	...	..	....
25	14 days	0.770	0.54	124	123	128	157	581	55	7.37
6	14 wks.	0.774	0.37	...	...	...	161	613	..	....
I	27 wks.	0.769	0.39	124	125	114	147	619	..	....
W	40 wks.	0.774	0.38	141	141	137	156	619	56	7.37
19	11 days	.....	....	...	94	86	144	619	56	7.40
7	14 wks.	0.778	0.25	...	...	...	158	595	55	7.40
VI	30 wks.	0.787	0.26	111	110	110	158	590	50	....
W	40 wks.	0.780	0.26	113	112	107	151	586	56	7.40
31	5 days	0.782	0.31	103	103	107	157	589	56	7.37
	13 days	0.765	0.38	125	127	130	154	585	58	7.40
8	14 wks.	0.773	0.36	...	...	...	154	613	..	....
III	28 wks.	0.793	0.30	94	92	89	150	589	..	....
C	40 wks.	0.795	0.31	102	100	99	153	613	51	7.40
30	11 days	.....	....	...	85	...	...	619	57	7.37
9	14 wks.	0.761	0.38	...	...	...	160	596	53	7.40
I	29 wks.	.....	....	...	127	122	...	619	..	....
C	40 wks.	0.774	0.42	131	129	92	151	619	..	....
21	3 days	0.780	0.43	95	94	89	147	601	..	....
	12 days	0.783	0.44	93	92	...	147	596	58	7.40
10	20 wks.	0.784	0.35	...	...	...	137	596	51	....
I	36 wks.	0.770	0.37	110	113	125	152	555	..	....
W	3 days	0.766	0.35	88	88	93	159	596	60	7.40
26										
11	15 wks.	0.778	0.40	...	...	...	157	619	..	....
I	28 wks.	0.802	0.38	105	102	97	149	619	55	7.37
W	39 wks.	0.765	0.35	100	102	101	155	625	46	7.40
22	12 days	0.762	0.37	93	94	91	150	590	55	7.40
12	9 wks.	0.789	0.40	...	...	...	151	560	53	....
I	27 wks.	0.775	0.40	131	133	128	145	625	59	....
C	40 wks.	0.768	0.28	99	102	101	149	625	56	....
28	11 days	0.776	0.32	99	98	99	151	601	57	....
13	11 wks.	.....	....	...	...	...	152	596	..	....
VIII	29 wks.	0.774	0.39	...	106	106	152	613	..	....
C	40 wks.	0.768	0.38	93	99	92	140	619	54	7.35
37	11 days	.....	....	...	92	95	144	607	55	7.40
22	16 wks.	0.788	0.42	...	...	...	149	613	..	....
II	28 wks.	0.773	0.34	93	95	...	149	613	53	7.40
W	40 wks.	0.784	....	...	...	...	152	625	..	....
24	12 days	0.781	0.34	...	...	...	151	619	..	....

* W = white; C = colored.
† mM. = millimols.

whether the p_H in pregnancy increases toward the alkaline side or shows no significant change. From repeated observations of p_H since 1925, we believe that in normal pregnancy no significant changes occur, and, furthermore, that it will require repeated determinations on the same patients throughout pregnancy to prove a change.

TABLE 11.—*Data on Patients Followed from Term to Eight Weeks Post Partum (Series B)*

Patient, Gravida, Color,* Age	Period of Gestation or Post Partum	Conductivity as Sodium Chloride			Plasma Volume Change,	Total Base		Sodium Chloride,	Carbon Dioxide,	
		Per Cent	Gm. per Kg.	Change, per Cent	per Cent	Change, per Cent	mM.†	Mg. per 100 Cc.	per Cent by Vol.	p_H
31	39 wks.	0.768	0.46	...	...	...	...	619	46	7.40
I	12 days	.....	....	...	64	...	164	613	60	7.40
C	8 wks.	.....	....	...	74	...	...	...	..	....
15										
32	40 wks.	0.736	0.38	...	...	...	...	590	56	7.40
I	3 days	0.770	0.34	81	77	...	...	590	57	7.37
W	12 days	0.774	0.60	135	82	...	157	590	58	7.40
27	8 wks.	0.782	0.35	87	82	...	170	589	..	....
33	40 wks.	0.785	0.29	...	...	...	158	625	58	....
II	3 days	0.785	0.33	98	98	89	144	607	49	....
W	19 days	0.787	0.31	89	89	91	161	589	..	....
29	9 wks.	0.802	0.36	106	104	104	158	625	..	....
34	40 wks.	0.803	0.40	...	...	...	153	619	..	....
I	5 days	0.795	0.33	71	72	79	168	610	54	7.40
C	8 wks.	0.803	0.39	88	88	86	149	630	..	....
25										
35	36 wks.	0.782	0.36	...	...	...	131	590	54	....
II	11 days	0.770	0.35	87	88	110	164	619	50	7.37
W	8 wks.	0.783	0.35	84	84	...	...	613	..	....
24										
36	40 wks.	0.768	0.35	...	...	...	...	543	42	....
I	3 days	0.768	0.42	110	110	...	...	590	35	....
C	12 days	0.782	0.37	88	86	...	...	619	53	....
25	8 wks.	.....	....	...	100	...	...	589	..	....
37	38 wks.	0.775	0.46	...	...	...	137	619	56	....
III	12 days	0.793	0.32	61	60	...	...	619	45	....
W	8 wks.	0.800	0.44	88	85	93	149	595	..	....
30										
39	39 wks.	0.759	0.40	...	...	...	...	543	53	....
I	11 days	0.785	0.33	69	67	...	...	613	59	....
W	17 wks.	0.814	0.31	63	59	...	157	625	..	....
17										
40	40 wks.	0.763	0.41	...	...	...	147	590	..	....
IV	3 days	0.763	0.45	96	96	96	146	578	..	....
C	25 days	0.784	0.49	102	100	104	153	596	..	....
28	8 wks.	0.790	0.40	85	82	96	172	613	50	....
43	38 wks.	0.775	0.40	...	...	...	159	625	..	....
V	5 days	0.766	0.32	70	71	67	151	578	..	....
C	19 days	0.800	0.52	113	110	100	144	595	..	....
17	8 wks.	0.789	0.40	87	86	83	154	578	..	....

* W = white; C = colored.
† mM. = millimols.

In table 9 are listed the variations and averages for serum sodium chloride. The variation is marked, but the averages show little change, with the exception of the first week post partum, when there is a slight decrease, amounting to from 10 to 15 mg. Harding and Van Wyck [4]

4. Harding, V. J., and Van Wyck, H. B.: Diet in Treatment of Pre-Eclampsia, J. Obst. & Gynec. Brit. Emp. **33**:17, 1926.

stated that the whole blood chlorides increase from the normal of 475 mg. per hundred cubic centimeters to a maximum of 518 mg. at the eighth lunar month, and then decrease to 490 mg. at term. Their results are based on a study of sixty-seven determinations. Our results, based on several hundred determinations, many of them on the same patients at different periods, indicate that there are no significant changes in the serum chlorides.

In table 10 are listed essential data for series A. The majority of the patients show a decrease in the conductivity and total base of the serum during pregnancy, which is most marked at term. Variations in total amount of these substances demonstrate definite increases, and calculation of each on a per kilogram basis also shows an increase, thus indicating that there is apparently an actual retention. The degree of change in total conductivity, total base and plasma volume is remarkably constant—a further proof of the fine balance maintained by the body. Carbon dioxide content and p_H determinations, while comparatively few, demonstrate that there is no acidosis in pregnancy. Serum chlorides show a wide fluctuation but no characteristic changes.

In table 11 are listed essential data for series B. In this group the observations extend from term to eight weeks post partum. Determinations of conductivity indicate a return to the normal at from six to eight weeks post partum. Observations on total base show such marked variations that no conclusions can be drawn. Variations in total amount show a decrease, and again they are of the same degree and direction as the changes in plasma volume. Determinations of carbon dioxide content, p_H and serum chloride are within the normal range.

CONCLUSIONS

The data for conductivity, total base, carbon dioxide content, p_H and chlorides, which have been reported in the literature for both normal nonpregnant and pregnant women, are based on a relatively small number of determinations. As a result, considerable confusion has arisen as to what changes, if any, occur in some of these constituents of the blood in pregnancy.

Determinations of these substances and, in addition, of plasma volume were made on various patients for the different periods of pregnancy. Similar studies were made on the same women by means of serial determinations at periodic intervals. The results were studied statistically, and the following conclusions are made: 1. The conductivity of the serum is decreased, reaching a minimum at term which is from 4 to 6 millimols below the normal, and it does not return to the normal until six to eight weeks post partum. This decrease, mean-

ing a decrease in the total electrolyte, predicates a decrease in the serum ash.

2. The conductivity expressed as grams of sodium chloride per kilogram shows no significant change.

3. The total base is decreased, reaching a minimum at term which is from 4 to 6 millimols below the normal. It does not return to the normal until two or three weeks post partum. The decrease in the total base is substantiated by the decrease in the conductivity, which can be determined more accurately than the total base.

4. The carbon dioxide content is decreased from 6 to 10 per cent by volume in pregnancy.

5. There are no significant changes of the p_H from the normal.

6. There is no acidosis of pregnancy, but the condition is one of a compensated alkali or carbon dioxide deficit.

7. Determinations for serum chloride show no significant change from the normal.

8. Variations in total amount of conductivity, expressed as percentage of sodium chloride and of total base, show an average increase at from twenty-six to thirty-five weeks of 16.8 and 18 per cent, respectively, and at term the average increases are 22.7 and 20.6 per cent. The increase in the individual cases is of the same magnitude as the plasma volume.

9. Similar studies with the addition of determinations of electrolyte metabolism on the same women during pregnancy are necessary before the mechanism of these various changes will be known.

10. A logical explanation of the decrease of electrolytes, serum protein, hematocrit values, etc., in pregnancy will be of inestimable value in solving many of the problems associated with edema.

STUDIES OF THE BLOOD IN NORMAL PREGNANCY

VI. PLASMA CHOLESTEROL IN MILLIGRAMS PER HUNDRED CUBIC CENTIMETERS, GRAMS PER KILOGRAM AND VARIATIONS IN TOTAL AMOUNT

WILLIAM J. DIECKMANN, M.D.
CHICAGO
AND
CARL R. WEGNER, M.D.
ST. LOUIS

Although many of the reports of determinations indicate that cholesterol is increased in pregnancy, there is still lack of agreement as to the time when the increase begins, the amount and the cause of the gain. Greater importance is being ascribed to cholesterol, as shown by the constantly increasing number of papers on this subject in the literature. It is not known just what part it plays in the permeability of membranes, edema, nephritis, nephroses, pregnancy, resistance to infection, epilepsy, etc., but sufficient data have been accumulated to indicate that a marked change in cholesterol is intimately associated with these conditions, which undoubtedly are either the cause or the result of the change.

Cholesterol is found in both the erythrocytes and the plasma, occurring as the free alcohol and also as the ester of the fatty acids. In addition, certain other combinations or adsorption products of cholesterol and serum protein have been described. A noteworthy fact is that in the new-born baby cholesterol is present only in the free form.

In table 1 are listed data for plasma and whole blood total cholesterol (free and combined) in nonpregnant and pregnant women. The range for plasma cholesterol in the nonpregnant woman is from 80 to 250 mg. per hundred cubic centimeters, with an average of 175 mg., and for whole blood it is from 98 to 250 mg., with an average of 184 mg. In pregnancy the range for plasma is from 130 to 426 mg. per hundred cubic centimeters, with an average of 234 mg., while the range for whole blood is from 84 to 640 mg. with an average of 241 mg.

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From the Department of Obstetrics and Gynecology, Washington University School of Medicine, the St. Louis Maternity Hospital, the Department of Obstetrics and Gynecology, the University of Chicago, and the Chicago Lying-in Hospital and Dispensary.

The variations in the amount of cholesterol are extremely wide, and several explanations are possible: (1) Exact methods have been perfected only recently; (2) cholesterol may show rather wide variations hourly; (3) long continued alterations in diet may cause changes, and

TABLE 1.—*Reported Averages for Total Cholesterol in Nonpregnant and Pregnant Persons* *

		Nonpregnant			Pregnant		
	Year	No. of Determinations	Range, Mg. per 100 Cc.	Average, Mg. per 100 Cc.	No. of Determinations	Range, Mg. per 100 Cc.	Average, Mg. per 100 Cc.
Herrmann and Neumann..... (Biochem. Ztschr. **43**: 47 1912)	1912	..	130-170	144	..	.....	181
Klinkert ..... (Berl. klin. Wchnschr. **50**: 820, 1913)	1913	17	130-275 P†	182	17	186-426 P	263
Bloor and Knudson..... (J. Biol. Chem. **29**: 7, 1917)	1917	6	184-208	193	3	181-250-291	240
Slemons and Curtis..... (Am. J. Obst. & Gynec. **75**: 569, 1917)	1917	..	.....	...	18	200-380	260
Denis ..... (J. Biol. Chem. **29-30**: 93, 1917)	1917	6	185-250	214	9	183-283	236 (no change)
Pribram ..... (Arch. f. Gynak. **119-120**: 57, 1923)	1923	..	.....	...	15	84-640	252
Slemons and Stander..... (Bull. Johns Hopkins Hosp. **34**: 7, 1923)	1923	..	(200-250)‡	...	24	190-330	190
Bunker and Mundell..... (J. A. M. A. **83**: 836, 1924)	1924	..	(140-170)	...	72	155-220	190
Tyler and Underhill..... (J. Biol. Chem. **66**: 1, 1925)	1925	10	180-249	207	100	140-338	261
Moynihan ..... (Brit. M. J. **1**: 393, 1925)	1925	..	133-192 P	...	..	130-260 P	Increased
Oser and Karr..... (Arch. Int. Med. **36**: 507, 1925)	1925	18	105-246 P	187	6	200-300 P	260
Rosen and Krasnow..... (Am. J. Obst. & Gynec. **14**: 321, 1927)	1932	27	153-201	171±16	91	139-326	193
Okey and Boyden..... (J. Biol. Chem. **72**: 261, 1927)	1927	16	98-185	149	..	.....	...
Boyd and Roy (India)..... (Indian J. M. Research **15**: 643, 1928)	1927	..	82-184 P	...	..	.....	...
McClure and Huntsinger..... (J. Biol. Chem. **76**: 1, 1928)	1928	20	103-186	139	..	.....	...
Gardner and Gainsborough.... (Lancet **1**: 603, 1929)	1929	21	80-230 P	153	32	140-285 P	233
McEachern and Gilmour..... (Canad. M. A. J. **26**: 30 and 158, 1932)	1932	90	130-200 P	161	12	173-269	217
Gray and McGee..... (Arch. Neurol. & Psychiat. **28**: 357, 1932)	1932	29 M§	155-234	194±2.7 S.D. 22‖	..	.....	...
Bruger and Somack..... (J. Biol. Chem. **97**: 23, 1932)	1932	15	172-259	208	..	.....	...

* Determinations were made on whole blood.
† P denotes plasma.
‡ Parentheses indicates that the figures are assumed by the authors.
§ M denotes male.
‖ S.D. indicates standard deviation.

(4) with only one exception, all studies have been made on various groups of women for the different periods of pregnancy.

Bruger and Somack have shown, by hourly analyses of plasma cholesterol over a four-hour fasting period in nine normal subjects, that the standard deviation is ± 3.9 per cent, with limits of from ± 1.8

to ± 6.8 per cent. Similar determinations on whole blood were made every two hours for twenty-four hours in nine patients on standard diets, who were bedridden for various conditions. The cholesterol varied by a standard deviation of ± 8 per cent, with limits of variation of from ± 5.2 to ± 13.1 per cent. The data indicate that the higher the initial cholesterol level, the greater is the variation, but the standard deviations were practically the same for all cases. The ingestion of food had no constant effect, either immediate or late, on the cholesterol content of the blood.

McEachern and Gilmour made cholesterol determinations on whole blood on twenty-eight normal fasting persons. Blood was taken every hour for five hours. The standard deviation for their results, as calculated by Bruger and Somack, was ± 9.5 per cent, with limits of from ± 3.4 to ± 16.5 per cent. The authors concluded that such wide variations render single or haphazard studies of blood cholesterol of doubtful value. No evidence of cholesterol adsorption or of effect on the blood level was noted in twelve normal persons who were given large doses by mouth. A seasonal variation in the blood cholesterol of normal persons does not exist.

Gardner and Gainsborough,[1] who have carried out the most complete studies so far reported on cholesterol metabolism, concluded that during periods of fasting the cholesterol content of the plasma varies markedly in different healthy persons but is fairly constant in the subject himself; a single meal will cause no change, but prolonged diets, high or low in sterols, will cause variations in the cholesterol. The free cholesterol remains fairly constant, but the cholesterol ester shows the greatest changes. During the digestive process changes in the cholesterol content of the plasma occur frequently, at times as an increase and sometimes as a decrease, compared with the values during periods of fasting. Often a marked temporary disturbance of the ratio of the ester to the total cholesterol is observed. These peculiar changes must be regarded as evidence of an active endogenous metabolism, in which cholesterol takes part during digestion. The ester usually forms from 60 to 70 per cent of the total cholesterol.

Gray and McGee, who have made a study of cholesterol in normal, feebleminded and epileptic patients, reported that in the same subject the difference between two cholesterol determinations must be at least 40 mg. per hundred cubic centimeters to be considered of any significance and that meals affected the cholesterol only to a moderate degree.

McClure and Huntsinger determined whole blood cholesterol at hourly intervals in normal subjects before and after various meals.

1. Gardner, J. A., and Gainsborough, H.: Biochem. J. **19**:667, 1925; **21**:130, 1927; Quart. J. Med. **23**:465, 1930.

They concluded that the ingestion of all foods causes an increase in cholesterol, but that the gain is in a descending order for the foods listed: olive oil and oleic acid, dextrose and egg albumin. Hourly studies on the fasting subject show no marked changes, but determinations on the same subject at weekly or monthly intervals may demonstrate significant changes.

Thus, a study of the reports on cholesterol indicates that it remains fairly constant in the subject himself, although the range is rather great, and that it is not affected by food unless prolonged alterations in diet are maintained. For the individual subject, the change in cholesterol, to be of any significance, should be at least 40 mg. per hundred cubic centimeters.

Moynihan, in 1925, reported the work of Shiskins which indicated that the cholesterol was increased approximately 30 per cent just preceding and during the first one or two days of the menstrual period.

Okey and Boyden, who made over two hundred serial analyses of whole blood cholesterols during periods of fasting, covering twenty-six monthly cycles in sixteen women, concluded that the most striking and consistent cyclic alteration observed in the lipid content of the blood was the fall in blood cholesterol, which took place almost invariably during or within a few days of the menstrual period. This was usually preceded or followed by levels for blood cholesterol which were higher than the averages for the persons concerned. Since the initial rise in the cholesterol level, the menstrual fall and the postmenstrual rise, with the secondary fall to approximately the average level, require two weeks or more for completion, it will be seen that the level for blood cholesterol in women is to be considered as a variable rather than a constant factor. Thus, cholesterol is subjected to additional influences in women because of the cyclic changes of the endocrine glands, and the range is thereby increased.

The wide ranges for the averages in pregnancy, listed in table 1, indicate that this condition produces even more marked alterations.

Kehrer,[2] basing his opinion on the reports of two investigators, concluded that in pregnancy there is a hypercholesteremia which begins in the third month and increases as the pregnancy progresses. He stated that the increased amount of cholesterol explains the fact that pregnant women require less ether or chloroform than nonpregnant women (the absorption of these anesthetics is increased by the high levels of lipid).

Denecke,[3] also basing his opinion on essentially the same authors as Kehrer, concluded that the free and ester cholesterol of the blood

2. Kehrer, E., quoted in Halban, Joseph, and Seitz, Ludwig: Biologie und Pathologie des Weibes, Berlin, Urban & Schwarzenberg, 1926, vol. 6, p. 813.

3. Denecke, G., quoted in Hinselmann, H.: Die Eklampsie, Bonn, Friedrich Cohen, 1924.

are increased in pregnancy, owing to a decreased excretion in the bile. After delivery they are excreted rapidly in the milk, urine and bile, and by the end of the second week post partum the cholesterol level is normal.

Tyler and Underhill determined whole blood cholesterol in normal persons, and in pregnant women. They studied ten women in each month of pregnancy, beginning with the third, and reported that cholesterol and ester cholesterol increase gradually until term; at that time each is roughly one-third higher than at three months.

McEachern and Gilmour determined whole blood cholesterol in twelve pregnant women and concluded that a marked elevation is found in about 30 per cent of normal pregnant women, beginning about the sixth week prior to delivery, and that about 80 per cent have a level above normal on the first day after delivery. The figures are still high on the twelfth day post partum.

Gardner and Gainsborough made two or more serial determinations of total, free and ester cholesterol in eight women during pregnancy and one or more postpartum analyses in ten women, and concluded: 1. The free cholesterol of the plasma increases during pregnancy up to a maximum at about the thirtieth week; concurrently, the ester cholesterol falls to a minimum at about the same time. 2. From the thirtieth week, more or less approximately, the amount of free cholesterol decreases, and the ester cholesterol increases until an almost normal ratio of free to ester cholesterol is attained before or near parturition. 3. The values for plasma cholesterol are generally normal in the first week or two of the puerperium. 4. Some cases show a definite total hypercholesteremia in which the figures for total cholesterol run, roughly, parallel to the values for free cholesterol. During pregnancy there is a marked disturbance of the cholesterol metabolism, which results in great changes in the ratio of free to ester cholesterol in the plasma, but in less definite changes in the total cholesterol.

All of the investigators, with the exception of Denis who determined the blood cholesterol in nine pregnant women and stated that no increase was found, concluded that cholesterol is increased late in pregnancy, and many of them assumed that the increase is due either to a faulty elimination by the liver or to a retention preparatory for lactation.

METHOD

Determinations of plasma cholesterol and plasma volume, as described previously, were made on a number of women during pregnancy and the puerperium. One group, in which serial determinations were made on the same women during pregnancy and the puerperium, is designated as series A. A second group, designated as series B, was followed from term to eight weeks post partum. The total number of

cases includes both series, with the addition of many single analyses. The determinations for cholesterol were made on plasma which had been obtained as previously described. Leiboff's method was used. Only total cholesterol could be determined because of the volume of work, but it was believed that if changes did occur, either in free or in ester cholesterol, they would be of sufficient magnitude to affect the total.

In table 2 are listed the variations and means for plasma cholesterol during pregnancy and the puerperium. The difference between the means of the total cases for the first trimester and for term is signifi-

TABLE 2.—*Plasma Cholesterol, Milligrams per Hundred Cubic Centimeters: Variations and Means in Pregnancy and the Puerperium*

	Number of Patients							
	Ante Partum, Weeks				Post Partum, Days			
Range, Mg. per 100 Cc.	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 15	18 to 26	8 to 17 Weeks
128-199	5	1	1	5	2	3	1	2
200-249	4	3	4	7	2	8	5	2
250-299	5	2	4	4	4	3	3	3
300-349	6	2	9	11	7	6	1	1
350-399	2	1	3	12	3	1	..	1
400-449	1	..	2	5	3	5	1	..
450-549	..	..	..	5	..	2	..	..
Total	23	9	23	49	21	28	11	9
	Means							
Total cases	269.5 ± 11	.....	307.6 ± 8.9	331.1 ± 9.4	310.7 ± 11.3	307.1 ± 10.6		
Standard deviation	78.5	.....	63.5	97.0	76.5	102.5		
Series A	263	...	289	268	...	248		
Series B	...	...	...	348	354	338	282	254

cant, amounting to an increase of 23 per cent. The slight variation for series A is due to the relatively small number of patients and to the marked individual variations. Series B shows a decrease of 27 per cent at eight weeks post partum. Our data, calculated either as the increase in the number of high cholesterols or as averages, demonstrate definitely that pregnancy is characterized by a hypercholesteremia, and that this condition not only begins early in pregnancy but is still present eight weeks post partum.

In table 3 are listed the variations and means for the grams of cholesterol per kilogram. The plasma volume multiplied by the milligrams of cholesterol per hundred cubic centimeters, and the product divided by the body weight equals the grams of cholesterol per kilogram. The increase is even more striking and at term amounts to 33 per cent, while at eight weeks post partum there is a decrease amounting to 39 per cent.

In table 4 are listed the changes in the percentage of total circulating cholesterol during pregnancy and the puerperium. The total cholesterol was determined by multiplying the plasma volume by the milligrams of cholesterol per hundred cubic centimeters. The first determination

TABLE 3.—*Plasma Cholesterol, Grams per Kilogram: Variations and Means in Pregnancy and the Puerperium*

	Number of Patients							
	Ante Partum, Weeks				Post Partum, Days			
Range, Gm. per Kg.	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 15	18 to 26	8 to 17 Weeks
0.050-0.099	7	..	2	5	2	4	2	3
0.100-0.149	13	4	11	14	8	12	7	3
0.150-0.199	3	2	7	17	10	9	1	4
0.200-0.249	2	..	3	4	1	2	..	..
0.250-0.300	..	..	..	7	..	1	..	..
Totals	25	6	23	47	21	28	10	10
	Means							
Total cases	0.123 ± 0.006	.....	0.148 ± 0.006	0.169 ± 0.006	0.151 ± 0.005	0.146 ± 0.007		
Standard deviation	0.041	.....	0.039	0.063	0.036	0.051		
Series A	0.118	.....	0.136	0.130	.....	0.129		
Series B	.. ..	.....	.....	0.178	0.167	0.152	0.131	0.126

TABLE 4.—*Average Changes in Plasma Cholesterol Calculated on the Basis of Total Amount* *

	Ante Partum				Post Partum					
	26-35 Weeks		36-40 Weeks		2-6 Days		10-25 Days		8-17 Weeks	
	No. of Cases	Change, per Cent	No. of Cases	Change, per Cent	No. of Cases	Change, per Cent	No. of Cases	Change, per Cent	No. of Cases	Change, per Cent
Average increase for all patients	13	33.9	14	27.9	..	....	..	....	..	....
Average increase for those showing increase	8	62.8	9	55.8	6	28.8	7	36.7	1	40.0
Average decrease for all patients	..	....	..	....	19	11.8	35	15.0	10	21.2
Average decrease for those showing decrease	2	35.5	5	22.4	9	44.2	23	34.1	8	31.2
No change	3	0	0	0	4	0	5	0	1	0

* The initial determination is used as 100 per cent for the antepartum period, and the last antepartum determination as 100 per cent for the postpartum period.

was assumed to be 100 per cent, and all others during pregnancy were divided by it and the dividend multiplied by 100. Determinations after delivery were converted similarly, using the figure found at term as the divisor. Thus all data were converted to a common factor and could be compared. At from twenty-six to thirty-five weeks' gestation there was an average increase of 33.9 per cent in cholesterol. At term the average increase was 27.9 per cent. Five cases showed an increase of 55.8 per cent, and five, a decrease of 22.4 per cent. Changes of ± 4 per

TABLE 5.—*Data on Patients Followed Throughout Pregnancy and the Puerperium (Series A)*

Patient, Gravida, Color,* Age	Period of Gestation or Post Partum	Plasma Cholesterol				Plasma Volume Change, per Cent
		Mg. per 100 Cc.	Gm. per Kg.	Total Amount, Gm.	Change, per Cent	
1	13 wks.	333	0.134	6.22	...	...
II	29 wks.	370	0.206	11.49	185	166
W	40 wks.	303	0.196	11.68	188	206
20	12 days	222	0.153	7.72	66	90
2	14 wks.	158	0.060	4.64	...	...
I	30 wks.	233	0.097	7.85	169	115
W	40 wks.	158	0.068	5.50	119	119
23	12 days	148	0.059	4.32	79	86
3	15 wks.	345	0.193	10.27	...	...
I	30 wks.	345	0.210	12.83	125	125
W	40 wks.	238	0.129	8.19	80	116
23	12 days	333	0.197	10.45	128	91
4	14 wks.	150	0.049	4.51	...	...
VII	27 wks.	333	0.133	12.22	271	122
W	40 wks.	150	0.069	6.00	133	133
30	14 days	...	.....	.....	...	75
5	12 wks.	333	0.133	7.11	...	...
II	28 wks.	263	0.122	7.25	102	129
W	39 wks.	...	.....	.....	...	140
25	14 days	...	.....	.....	...	123
6	14 wks.	...	.....	.....	...	...
I	27 wks.	338	0.170	9.32	...	125
W	40 wks.	218	0.107	6.77	73	141
19	11 days	230	0.119	6.69	99	94
7	14 wks.	266	0.086	9.19	...	...
VI	30 wks.	370	0.124	14.00	152	110
W	40 wks.	385	0.130	14.95	163	112
31	5 days	357	0.142	14.28	96	103
	13 days	380	0.187	18.76	125	127
8	14 wks.	434	0.202	18.74	...	...
III	28 wks.	200	0.076	7.90	42	92
C	40 wks.	358	0.139	15.18	81	100
30	11 days	...	.....	.....	...	85
9	14 wks.	239	0.120	5.98	...	...
I	29 wks.	194	0.105	6.15	103	127
C	40 wks.	312	0.168	10.08	169	129
21	3 days	326	0.178	9.93	99	94
	12 days	302	0.170	8.96	89	92
10	20 wks.	333	0.149	10.67	...	...
I	36 wks.	372	0.177	13.39	125	113
W	3 days	337	0.152	10.72	80	88
26						
11	15 wks.	238	0.122	8.19	...	...
I	28 wks.	313	0.149	11.01	134	102
W	39 wks.	333	0.153	11.71	143	102
22	12 days	250	0.121	8.25	70	94
12	9 wks.	150	0.075	4.61	...	...
I	27 wks.	...	.....	.....	...	133
C	40 wks.	333	0.121	10.45	227	102
28	11 days	272	0.111	8.37	80	98
13	11 wks.	244	0.128	8.73	...	...
VIII	29 wks.	200	0.101	7.62	87	106
C	40 wks.	194	0.097	6.90	79	99
37	11 days	224	0.113	7.39	107	92
22	16 wks.	...	.....	.....	...	...
II	28 wks.	312	0.139	8.91	...	95
W	40 wks.	190	.....	.....	...	...
24	12 days	128	0.056	3.38	38	93

* W denotes white race; C, colored race.

cent were listed as "no change." After delivery there was a constant decrease amounting to 21.2 per cent at eight weeks, which is not quite equal to the increase.

In table 5 are listed essential data for series A. Despite the marked fluctuations of cholesterol there was an average increase of 33 per cent

TABLE 6.—*Data on Patients Followed from Term to Eight Weeks Post Partum (Series B)*

Patient, Gravida, Color,* Age	Period of Gestation or Post Partum	Plasma Cholesterol				Plasma Volume Change, per Cent
		Mg. per 100 Cc.	Gm. per Kg.	Total Amount, Gm.	Change, per Cent	
31	39 wks.	361	0.216	14.44	...	...
I	12 days	174	0.079	4.46	31	64
C	8 wks.	...	.....	.....	..	74
15						
32	40 wks.	357	0.183	11.90	...	...
I	3 days	357	0.159	9.20	77	77
W	12 days	435	0.215	11.93	100	82
27	8 wks.	333	0.150	9.08	76	82
33	40 wks.	410	0.154	15.90	...	...
II	3 days	432	0.182	16.42	103	98
W	19 days	277	0.109	9.57	60	89
29	9 wks.	384	0.174	15.50	97	104
34	40 wks.	...	.....	.....	...	...
I	5 days	...	.....	.....	...	72
C	8 wks.	158	0.078	5.01	...	88
25						
35	36 wks.	381	0.176	12.01	...	...
II	11 days	500	0.226	13.91	116	88
W	8 wks.	345	0.156	9.16	76	84
24						
36	40 wks.	303	0.140	9.58	...	...
I	3 days	333	0.184	11.59	121	110
C	12 days	200	0.096	5.44	57	86
25	8 wks.	166	0.096	5.25	55	100
37	38 wks.	476	0.283	23.23	...	...
III	12 days	416	0.166	12.15	52	60
W	8 wks.	278	0.154	11.55	50	85
30						
39	39 wks.	333	.....	.....	...	...
I	11 days	303	0.127	6.57	...	67
W	17 wks.	238	0.091	4.54	69	59
17						
40	40 wks.	154	0.084	4.52	...	...
IV	3 days	238	0.139	6.72	149	96
C	25 days	294	0.184	8.60	190	100
28	8 wks.	263	0.134	6.33	140	82
43	38 wks.	361	0.186	13.40	...	...
V	5 days	411	0.170	10.82	81	71
C	19 days	223	0.146	9.09	68	110
17	8 wks.	200	0.103	6.35	47	86

* W denotes white race; C, colored race.

at term, with two patients showing no change. Further analysis of the data shows that there was an increase of 50 per cent in five patients and a decrease of 17 per cent in five. At twelve days post partum the values are still well above normal. The majority of the patients showed marked gains in total cholesterol and decreases at twelve days post partum. These changes in total cholesterol, suggesting a definite storage, indicate its importance but give no clue as to the reason.

In table 6 are listed essential data for series B. Marked fluctuations occur, but the tendency is for the values to decrease. The decrease in total cholesterol is of particular significance in that it indicates that the pregnancy was the stimulus for the increase.

COMMENT

What is the need for an increase in cholesterol in pregnancy? Is it a storage preparatory for lactation; is it a retention due to impaired elimination, or is it another manifestation of the disturbance in the chemical equilibrium of the blood caused by pregnancy? Pribram and others concluded that the increase is associated with a decreased excretion in the bile. However, we find the increase occurring early in pregnancy and persisting for weeks after delivery, which facts are not in accordance with the foregoing statement. Our findings, especially the persistence post partum, the irregularity in the amount of retention and the relatively small amount retained, would indicate that the increase is not a preliminary step in the preparation for lactation, as suggested by Slemons and Stander. If the tissue retention is of the same magnitude as the blood retention it is possible that the storage of cholesterol is necessary for lactation. To prove this point, studies of metabolism are necessary.

It seems to us that the same mechanism which is causing a decrease in serum protein analogous to nephritis and nephroses, a decrease in the carbon dioxide content analogous to diabetes, and an increase in fibrin—all of which conditions are associated with hypercholesteremia —causes the increase in cholesterol in pregnancy. Whether or not it exercises a protective influence cannot be determined. We have found a marked hypocholesteremia in patients who died because of severe vomiting of pregnancy and of puerperal infection. In both conditions, because of the starvation (high fat and protein) and damage to the liver one would expect a hypercholesteremia. Further investigations are necessary before the changes can be explained.

CONCLUSIONS

In individual subjects, both plasma and whole blood cholesterol remain fairly constant, although within rather wide limits, and they are not affected by food unless prolonged alterations in diet are maintained.

Determinations of plasma cholesterol and plasma volume were made on various groups of women and also on the same women for the different periods of pregnancy. The following conclusions are warranted: 1. The variations and range of cholesterol in the same woman during pregnancy may be tremendous. The majority show an increase, which is apparent at from ten to fifteen weeks' gestation.

2. There is an average increase of 23 per cent at term and a decrease of 27 per cent at eight weeks post partum.

3. Cholesterol calculated as grams per kilogram shows an increase of 33 per cent at term, and a decrease of 39 per cent at eight weeks post partum.

Variations in the total amount of cholesterol indicate an increase of 33.9 per cent at from twenty-six to thirty-five weeks of gestation, and an increase of 27.9 per cent at term. After delivery there is a constant decrease, amounting to 21.2 per cent at eight weeks post partum.

The increase in both the concentration and the total amount of cholesterol is probably not preparatory for lactation but is associated with other changes in the chemical equilibrium, which is so markedly disturbed in pregnancy. Further work is necessary to determine whether the increase in cholesterol in pregnancy is caused directly by the pregnancy or is the result of the other changes in the blood.

CONSTANCY OF IRON IN THE BLOOD PLASMA AND URINE IN HEALTH AND IN ANEMIA

ARTHUR MARLOW, M.D.
AND
F. H. L. TAYLOR, PH.D.
BOSTON

Clinical studies on the production of hemoglobin following the oral administration of iron indicate the physiologic activity of this substance in hypochromic anemia. Heath and his co-workers [1] have shown that in such patients the intramuscular injection of ferric ammonium citrate is followed by a rise in hemoglobin representing approximately a quantitative reappearance of the injected iron as hemoglobin. Their observations suggest that the action of iron on the production of hemoglobin is not vaguely "catalytic" but bears a quantitative relationship to the formation of hemoglobin. The interest of investigators is, therefore, logically directed to the question of absorption of iron, since the degree of absorption of a given iron compound obviously controls the amount of iron available for the regeneration of hemoglobin.

Unless complete experiments on iron balance are performed, studies of absorption based on the elimination of iron in the feces are profitless. This is due to the fact that in patients given large doses of iron by mouth the small amounts absorbed must be distinguished from the large amounts which pass unchanged through the intestinal tract. Furthermore, since iron is secreted into the intestinal contents, it is difficult to differentiate between nonabsorbed iron and that secreted into the intestinal tract from the body. It was thought, however, to be worth while to determine whether, following the oral administration of iron, this substance was increased in the plasma or the urine. It was decided also to study the urine to determine whether during periods of production of hemoglobin in anemic patients the iron over and above that converted into hemoglobin appeared in the urine. Since the amount of iron present in the blood plasma and the urine would of necessity be small, the pri-

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard) of the Boston City Hospital and the Department of Medicine of the Harvard Medical School.

The expenses of this investigation were borne in part by a gift to Harvard University from Smith, Kline and French Laboratories, Philadelphia.

1. Heath, C. W.; Strauss, M. B., and Castle, W. B.: Quantitative Aspects of Iron Deficiency in Hypochromic Anaemia, J. Clin. Investigation **11**:1293, 1932.

mary essential was the development of a method which was sufficiently accurate to be applicable to the relatively small samples which could be secured from anemic patients.

CHEMICAL METHODS

Glassware.—All apparatus was rendered free from iron by preliminary extraction with hydrochloric acid. In the interval between experiments, the apparatus was thoroughly washed with soap and water, rinsed with tap water, and finally rinsed with iron-free distilled water.

Reagents.—The reagents employed were: distilled water, redistilled in glass vessels; concentrated sulphuric acid, iron-free; potassium thiocyanate, highest purity, 10 per cent solution in iron-free distilled water; ethyl acetate, highest purity; standard iron wire (99.9 per cent pure iron), and trichloracetic acid, highest purity.

All reagents were submitted to analysis by the same procedure as that used in the determination of the iron content of the blood plasma and the urine. The maximum iron content permitted was always less than the experimental error of the method (0.002 mg.).

Standard Iron Solution for Determinations with Blood Plasma and Urine.—One hundred milligrams of metallic iron in the form of research purity iron wire was weighed and brought into solution with the smallest possible amount of iron-free concentrated hydrochloric acid, one part of acid to one part of distilled water being used. The solution was transferred quantitatively to a 1,000 cc. volumetric flask and diluted to volume. From this solution two standards were prepared. For the standard for urinalysis exactly 10 cc. of the stock solution was transferred to a 1,000 cc. flask, 10 cc. of concentrated sulphuric acid was added, and the contents were diluted to volume with distilled water. One cubic centimeter of this solution was equivalent to 0.001 mg. of iron. For the standard for analysis of blood plasma, 100 cc. of the stock solution was transferred to a 1,000 cc. flask, 10 cc. of sulphuric acid was added, and the contents were diluted to volume with distilled water. One cubic centimeter of this solution was equivalent to 0.01 mg. of iron.

PROCEDURE FOR ANALYSIS OF THE BLOOD

Five cubic centimeters of venous blood was drawn in a chemically clean glass syringe and transferred to a centrifuge tube to which one drop of a saturated solution of potassium oxalate had been added and dried. The blood was stirred gently with a glass rod and centrifugated at approximately 1,600 revolutions per minute for ten minutes. The plasma was then tested spectroscopically and discarded if evidence of hemoglobin was present.

Six cubic centimeters of distilled water was added to exactly 2 cc. of this plasma and thoroughly mixed. Two cubic centimeters of a 20 per cent solution of trichloracetic acid was added, shaken, and allowed to stand at least ten minutes. The resulting mixture was filtered on ashless filter paper. To exactly 5 cc. of filtrate in a 300 cc. Kjeldahl flask, 2 cc. of concentrated sulphuric acid and two small glass beads were added. The solution was then digested in the usual manner until about 0.5 cc. of colorless liquid remained in the flask. To exactly 1 and 2 cc. of standard iron solution were added 7 and 8 cc. of distilled water, respectively. After thorough mixing, 2 cc. of a 20 per cent solution of trichloracetic acid was added to each sample, which was then shaken and allowed to stand at least ten minutes. The standards were then digested in the same way as the

sample of blood plasma. After digestion was complete, the contents of the flasks were allowed to cool and the inside of each flask was carefully washed down with 20 cc. of hot distilled water. The contents of the flasks were thoroughly shaken, held at the boiling point for a few moments and allowed to cool. Into each flask 10 cc. of a 10 per cent solution of potassium thiocyanate was added. The contents of the flasks were shaken thoroughly and transferred immediately to 50 cc. volumetric flasks, each containing 10 cc. of ethyl acetate. The contents were shaken and diluted to the mark with distilled water. After the contents were shaken again, the ethyl acetate was allowed to layer out, and portions were removed by individual pipets to the cups of a microcolorimeter and compared with the standard iron solution set at 10 or 20.

PROCEDURE FOR URINALYSIS

All specimens of urine were collected directly into glass containers, and 1 cc. of concentrated sulphuric acid was added to each container with the one or two hour collections, and 2 cc. of acid, to each container with the twenty-four hour collections. This precaution was taken to preclude the possibility of an increasing alkalinity precipitating the iron from solution. The containers were thoroughly shaken before the samples were removed for analysis.

To 100 cc. of urine in a 300 cc. Kjeldahl flask, 10 cc. of iron-free concentrated sulphuric acid and two small glass beads were added. To two of the 300 cc. Kjeldahl flasks were transferred 5 and 10 cc. of the standard iron solutions equivalent to 0.005 and 0.01 mg. of iron, respectively. Ten cubic centimeters of concentrated sulphuric acid and two small glass beads were added. Sufficient distilled water was added to make the total volume 60 cc. The samples and standards were digested in the usual manner. The digestion was continued until about 0.5 cc. of colorless liquid remained. The contents of the flask were cooled, and the inside of each flask carefully washed down with hot, distilled water; the contents were then thoroughly shaken and held at the boiling point for a few moments. The contents were again cooled, and 10 cc. of 10 per cent potassium thiocyanate solution added to each flask. After being shaken thoroughly, the contents were transferred rapidly to 100 cc. volumetric flasks containing 10 cc. of ethyl acetate each. They were shaken thoroughly and diluted to the mark with distilled water. They were again shaken, and the layers of ethyl acetate were removed by individual pipets to the cups of a microcolorimeter. The standard was set at 10.

Accuracy of Method.—From a study of recoveries from solutions of iron in distilled water, blood plasma and urine, it has been found that the lower limit of accuracy of this modified thiocyanate method is 0.002 mg. of iron.

EXPERIMENTAL PROCEDURES

The Blood Plasma Iron Content.—The observations recorded here are based on a study of the iron content of the plasma of five normal persons, of three patients suffering from anemia due to chronic loss of blood with achlorhydria and of two patients with pernicious anemia. The general results of the investigations are given in the table.

Blood was taken from a normal man immediately before the oral administration of 6 Gm. of ferric ammonium citrate, and subsequent samples, three, seven and eleven hours afterward. Chart 1 illustrates the entirely negative effect of the ingestion of the compound on the

Results of Experimental Study

Case	Type of Anemia	Blood Condition (Control Period)			Amount of Iron and Ammonium Citrate per Day	Blood Condition (Treatment Period)			Reticulocytes at Peak of Their Response to Iron, per Cent
		Hemoglobin, Gm. per 100 Cc.	Red Blood Cells, Millions per C.Mm.	Plasma Iron, Mg. per 100 Cc.		Hemoglobin, Gm. per 100 Cc.	Red Blood Cells, Millions per C.Mm.	Plasma Iron, Mg. per 100 Cc.	
Controls	Five normal persons without anemia	15.6	4.5 to 5.5	0.47*	None	15.6	4.5 to 5.5	0.47*	...
1	Chronic loss of blood (achlorhydria)	3.4 (a) to 5.0 (b)	1.9 (a) to 2.1 (b)	0.43† (mean of 13 determinations)	6 Gm. for 24 days	5.0 (a) to 11.5 (b)	2.1 (a) to 4.2 (b)	0.41† (mean of 46 determinations)	8.2
2	Chronic loss of blood (achlorhydria)	5.9 (a) to 5.0 (b)	3.0 (a) to 2.3 (b)	0.38† (mean of 18 determinations)	6 Gm. for 40 days	5.0 (a) to 11.7 (b)	2.3 (a) to 5.0 (b)	0.42† (mean of 68 determinations)	4.0
3	Chronic loss of blood (carcinoma of stomach)	5.1 (a) to 5.0 (b)	2.4 (a) to 2.2 (b)	0.42† (mean of 3 determinations)	6 Gm. for 13 days	5.0 (a) to 7.8 (b)	2.2 (a) to 3.2 (b)	0.48† (mean of 20 determinations)	8.6
4	Pernicious‡	9.4 (a) to 11.2 (b)	2.6 (a) to 2.8 (b)	0.44† (mean of 9 determinations)	6 Gm. for 21 days‖	11.2 (a) to 14.0#(b)	2.8 (a) to 2.9 (b)	0.47† (mean of 40 determinations)	No response
5	Pernicious¶	5.6 (a) to 9.3 (b)	1.3 (a) to 2.1 (b)	0.48† (mean of 9 determinations)	6 Gm. for 21 days	9.3 (a) to 12.9#(b)	2.2 (a) to 2.9 (b)	0.56† (mean of 30 determinations)	No response

* Based on an average of at least two determinations. Variation between duplicates not greater than 0.04 mg. Individual variation from 0.40 to 0.54 mg. per hundred cubic centimeters of plasma.

(a) Initial value for period.

(b) Final value for period.

† Variations occurred in daily iron values but within limits of experimental error.

‡ Slight reticulocyte (4 per cent) response to a weakly potent liver preparation prior to this investigation.

‖ Liver therapy discontinued seven days prior to institution of iron therapy.

Increase not to be attributed to iron. (Delayed response to liver.)

¶ Previous adequate response (19 per cent) to liver therapy, which was discontinued prior to institution of iron therapy.

level of the plasma iron. In addition, daily determinations of iron were made on the blood plasma of this subject for twenty-one days following the single dose of ferric ammonium citrate. No change occurred in the level of iron. The subject then took 6 Gm. of ferric ammonium citrate daily, and the level of the blood plasma iron was followed for three days, without any significant change being encountered. Five grams of powdered ferrous carbonate was then substituted for the ferric ammonium citrate, and the level of the iron was followed for twenty-one days. It fluctuated between 0.42 and 0.52 mg. per hundred millimeters of plasma and averaged 0.46 mg. Since the average of the control period was 0.39 mg. and normal variations of 0.2 have been encountered, it seems reasonable to conclude that prolonged administration of iron did not result in an increase of the plasma iron.

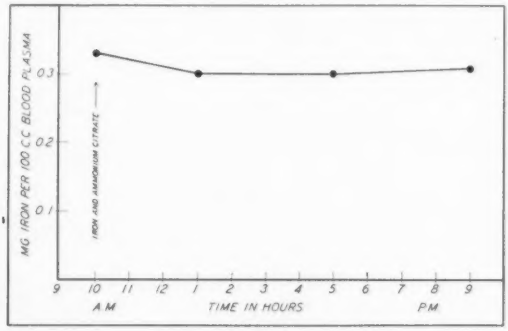

Chart 1.—The negative effect of the oral administration of 6 Gm. of iron and ammonium citrate on the iron content of the blood plasma of a normal person.

Three patients with hypochromic anemia due mainly to chronic loss of blood were studied. The results are shown in the table. Gastric achlorhydria was present in each of the three cases; prolonged dietary deficiency had existed in case 2, and carcinoma of the stomach was present in case 3. These various factors contributed to the degree of the anemia. A control period of from three to eight days was established during which time complete hematologic studies and determinations of iron were made, and the same observations were conducted daily throughout the period of treatment. The table shows that there was a prompt response of the bone marrow to the iron as indicated by the reticulocyte response and the lessening of the anemia. In cases 1 and 2 the hemoglobin increased by about 6 Gm. in four weeks. In case 3 the period of observation comprised only thirteen days, but here also a definite response occurred. In each case, however, the level of iron in the plasma remained remarkably constant during the entire period.

The results of the observations made on the two patients with pernicious anemia were similar to those on the patients with hypochromic anemia. The observations were made soon after a satisfactory reticulocyte response to liver therapy. The liver therapy was discontinued a few days prior to the control periods of seven and five days, respectively, for each case. At the conclusion of these control periods, the patients were given daily 6 Gm. of ferric ammonium citrate, and hematologic observations together with determinations of the level of iron in the blood plasma were made daily for twenty-one days. The slight increase in red cells and hemoglobin may be interpreted as due to the previous liver therapy. There was, as is shown in the table, no corresponding increase in the amount of plasma iron.

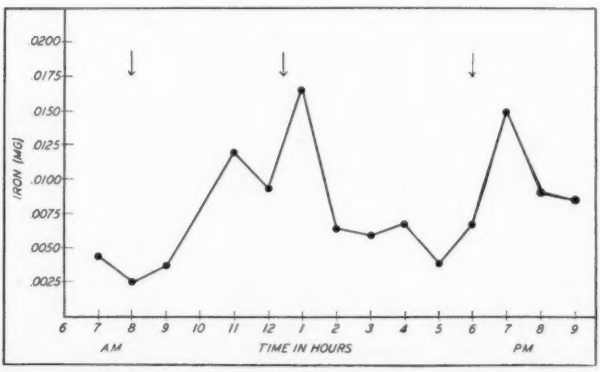

Chart 2.—The hourly excretion of iron in the urine of a normal person. The food intake is designated by arrows.

Excretion of Iron in the Urine.—The urine of two normal persons not given iron showed the average hourly excretion of iron to be 0.0026 and 0.0066 mg., respectively. The amount varied between 0 and 0.0133 mg. per hour for one person and between 0.0025 and 0.0170 mg. for the other. In every observation made on these subjects slight increases in the output of iron occurred before or after the ingestion of food. Chart 2 records a typical curve for one of these subjects. For purposes of comparison, chart 3 is presented to show the urinary excretion of iron in the same person when food was omitted. A conceivable explanation of the differences between the two curves is that slightly more iron was released to the urine owing to the secretion into the stomach of hydrochloric acid following ingestion of food. In the presence of this acid the absorption of iron was probably increased.

Since Mettier and Minot [2] previously reported the enhanced effect of iron administered in acid mediums, the foregoing observation suggested an investigation of the effect of administering iron in an acid medium on the urinary excretion of the substance. Hourly specimens of urine were obtained from 6 a. m. to 11 p. m. No food was taken

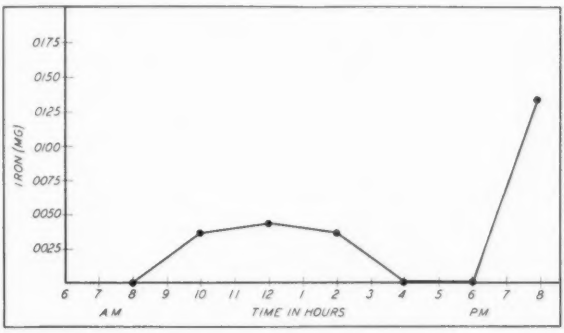

Chart 3.—The excretion of iron in the urine of a fasting normal person.

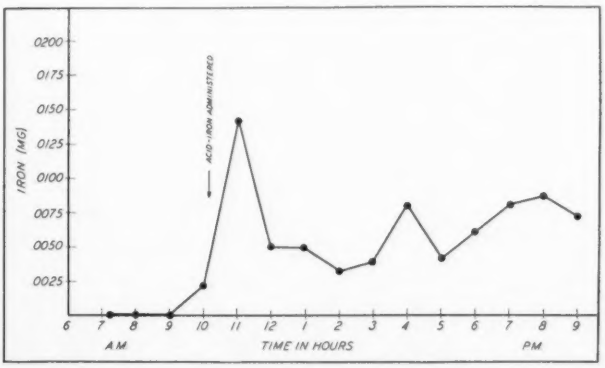

Chart 4.—The effect of the administration of iron in an acid medium on the hourly excretion of iron in the urine of a fasting normal person.

from 6 p. m. on the day preceding the experiment until shortly after 9 p. m. on the day iron was administered. Six grams of ferric ammonium citrate in aqueous solution was added to a beefsteak digestion

2. Mettier, S. R., and Minot, G. R.: The Effect of Iron on Blood Formation as Influenced by Changing the Acidity of the Gastroduodenal Contents in Certain Cases of Anemia, Am. J. M. Sc. **181**:25, 1931.

mixture, prepared as described by Mettier and Minot. The reaction of the mixture was p_H 3. The material was introduced into the stomach by tube at 9:50 a. m. The curve given in chart 4 represents the hourly excretion of iron in the urine under these conditions. The maximum excretion of iron occurred at 11 a. m., or fifty minutes after the introduction of iron and food with an acid reaction. Although greater variations than indicated in chart 4 have been encountered in untreated normal persons, the finding takes on significance when compared with the hourly excretion of iron in the urine of the same person in the absence of food, and after iron therapy as indicated in chart 3.

The excretion of iron in the urine of the patients with hypochromic anemia and pernicious anemia under iron therapy did not vary markedly from that found in normal persons given no iron. The total elimination of iron in the urine of the normal persons was found to vary between 0.06 and 0.1 mg. per twenty-four hours; in that of the three patients with hypochromic anemia under iron therapy, it fluctuated between 0.02 and 0.05 mg. per twenty-four hours, and in that of the two persons with pernicious anemia, it fluctuated between 0.037 and 0.59 mg.

COMMENT

Studies of the iron content of whole blood and blood serum are recorded in the literature, but little definite information has been available concerning the amount of iron in the blood plasma of man. Riecker [3] studied the iron content of serum and gives as an average normal figure 1 mg. per hundred millimeters of blood. McIntosh [4] recently established a value of from 0.5 to 1 mg. per hundred millimeters of blood for what he calls the "non-protein iron of the blood." Changes in the values of whole blood iron indicate essentially alteration in the hemoglobin content of the blood, and do not reflect changes in the small amount of extracellular iron in the plasma. It is of interest to note that McIntosh ascribed the greater part of his "nonprotein" iron to the cell, in loose combination with hemoglobin. It has been shown that a quantitative relationship exists between the absorbed iron and the increase in hemoglobin.[1] To the blood plasma has been ascribed the function of transportation of the iron. Such a function does not seem to predicate an increase in the amount of iron in the plasma. In contradistinction to Riecker, our daily study on the plasma iron of patients with hypochromic anemia passing through a remission due to iron therapy showed no increase in the amount of iron. Nor do the

3. Riecker, H. H.: Iron Metabolism in Pernicious and in Secondary Anemia, Arch. Int. Med. **46**:458 (Sept.) 1930.

4. McIntosh, J. F.: The Nonprotein Iron of the Blood, J. Clin. Investigation **12**:967, 1933.

data show any increase in the amount of plasma iron with an increase in the level of hemoglobin. This sharply differentiates the observations of this investigation from the findings of McIntosh with respect to "nonprotein" iron. Although only three cases of hypochromic anemia were studied, the observations were controlled, and from twenty to seventy determinations of plasma iron were made in each case. The evidence indicates that the level of the plasma iron during the control period did not vary essentially from that found for normal persons. Prolonged and effective iron therapy did not materially affect the level of the iron in the blood plasma. Coincident increases in the total amount of blood iron, as evidenced by considerable increase in the level of hemoglobin, failed to produce a parallel increase in the level of plasma iron. On the basis of this evidence, one must conclude that the deficiency of iron in hypochromic anemia is not manifest in the blood plasma. This finding bears a close parallelism to what occurs so often in depletion of calcium. Decalcification of bone may progress to an alarming extent without decrease in the level of the serum calcium. There seems to exist a similar state of affairs in the case of plasma iron. The constancy of the plasma iron level in the patients studied was remarkable. In all probability the increase in hemoglobin during remission accounts for almost all of the iron effectively utilized by the organism.[1]

The investigations on the iron content of the urine differ from previous comparative studies in that shorter intervals of time have been used. This method of investigation was adopted since evidence has been gradually accumulating which tends to show that the absorption of iron may be influenced significantly by the degree of acidity of the gastro-intestinal tract.[2] The changes caused by ingestion of food or by changes in the acidity of the upper part of the gastro-intestinal tract are assuredly better studied by determining the excretion of iron in the urine from hour to hour than at longer intervals. The amount of iron found in the urine of normal persons and of persons with anemia was somewhat lower than that reported by Riecker [3] but in close agreement with the figures given by Henriques and Roland,[5] and more recently by Bassett.[6] In Bassett's study the analyses were made by an electrometric method.

Examination of the data obtained seems to show a somewhat greater excretion of iron at the time food was ingested and following the administration of iron in an acid medium. It must be remembered, however, that in the study of the effect of acid the persons studied were in

5. Henriques, V., and Roland, H.: Zur Frage des Eisenstoffwechsels, Biochem. Ztschr. **201**:479, 1928.

6. Bassett, S. H.: Personal communication to the authors.

normal health with respect to red blood cells and hemoglobin, and presumably had a satisfactory iron balance, and that in this investigation the iron was administered to patients by the oral route. Our results are in close agreement with those of Henriques and Roland, in that these authors found no characteristic changes in the output of iron in the urine of patients with "secondary" anemia. No attempt was made to study the excretion of iron administered parenterally. It is necessary in considering the results obtained in the two cases of pernicious anemia to bear in mind that the patients had already responded to liver therapy.

The data obtained from this investigation seem to warrant the conclusions.

CONCLUSIONS

1. The iron content of the blood plasma of normal persons varies between 0.4 and 0.7 mg. per hundred cubic centimeters, while that of the urine ranges from 0.03 to 0.8 mg. per twenty-four hours.

2. The iron content of the blood plasma and urine of three patients with hypochromic anemia due mainly to chronic loss of blood and of two patients with pernicious anemia soon after remission had been inaugurated was found to vary within normal limits. The oral administration of ferric ammonium citrate to these patients and to normal persons caused no definite increase in the iron content of the blood plasma or of the urine. However, in the normal person studied there was perhaps a slight increase in the urinary excretion of iron following the oral administration of this substance in an acid-buffered medium.

Miss Eleanor R. Shea, A.B., and Miss Marion Duane assisted in the technical work.

CONGESTIVE HEART FAILURE

XVIII. CLINICAL TYPES OF NOCTURNAL DYSPNEA

W. G. HARRISON, JR., M.D.

J. A. CALHOUN, M.D.

AND

T. R. HARRISON, M.D.

NASHVILLE, TENN.

The dyspnea of cardiac disease is a complex symptom occurring under a variety of circumstances and producing a multiplicity of clinical syndromes. Except for the dyspnea produced by exertion one rarely sees the various types in "pure" form because the same patient is likely to have at the same time several different kinds of dyspnea, and as the disease progresses new types develop while the old ones do not subside.

Elsewhere we have published studies in which attempts were made to achieve a more exact understanding of the pathogenesis of orthopnea [1] and of the dyspnea produced by exertion.[2] In this and in succeeding papers similar efforts will be directed toward an elucidation of nocturnal dyspnea. The literature on this subject is voluminous and is complicated by the fact that there is no general agreement on nomenclature. Because of this confusion in terms we prefer to use in the following review the phrase "nocturnal dyspnea," and by this term we designate the types of respiratory distress that are likely to be especially frequent and severe at night.

THEORIES REGARDING THE PATHOGENESIS OF DYSPNEA

Although many different hypotheses have been advanced as to the pathogenesis of nocturnal dyspnea, most of them are variants or combinations of a few main theories.

Back Pressure.—This hypothesis seems to have been the first of the various theories to receive serious support of an experimental nature. William H. Welch,[3] in whose contribution references to the earlier literature may be found, showed in 1878 that edema of the lungs could be produced in rabbits by ligation of the descending aorta, the branches

From the Department of Medicine, Vanderbilt University.

1. Harrison, T. R.; Calhoun, J. A.; Cullen, G. E.; Wilkins, W. E., and Pilcher, C.: J. Clin. Investigation **11**:133, 1932.

2. Harrison, T. R.; Harrison, W. G.; Calhoun, J. A., and Marsh, J. P.: Arch. Int. Med. **50**:690 (Nov.) 1932.

3. Welch, W. H.: Virchows Arch. f. path. Anat. **72**:375, 1878.

of the aortic arch and of most of the pulmonary veins. As a result of his experiments he concluded that pulmonary edema in man was to be regarded as secondary to a difference in the amount of blood pumped by the two ventricles, i. e., as due to back pressure from a dilated left ventricle which failed to empty itself sufficiently. In 1885, Sahli [4] made similar observations on dogs and was unable to produce pulmonary edema regularly. He concluded that there were other factors in addition to the mechanical ones. Forty years later, Kraus [5] found that pulmonary edema occurred in animals only when both ventricles were working energetically; often when the left ventricle was working poorly there was no pulmonary edema.

The findings of Eppinger, von Papp and Schwarz [6] were in general agreement with the back pressure hypothesis. These authors concluded as the result of their extensive study that two factors played a rôle in the production of the paroxysms of nocturnal dyspnea: diminished reserve power of the left ventricle and increased venous return to the heart due to peripheral vasodilatation. The result of these two factors operating simultaneously was considered to be an acute congestion of the lungs. This in turn caused the dyspnea, not by producing alterations in the composition of the blood, but by reflex stimulation of breathing. The authors did not demonstrate the existence of such reflexes but assumed them to be present and effective.

The same investigators were interested in the question as to why in many patients the attacks occurred so soon after the onset of sleep. They pointed out that in some patients dreams seemed to be the precipitating factor, but they did not believe that dreams were responsible in all instances. They found that the consumption of oxygen reached its lowest level within the first two hours after the onset of sleep and quoted the observations of Katsch and Pansdorf,[7] who found that the same was true of the blood pressure. The brain volume and pulsations, measured by plethysmographic methods on subjects with defects in the skull, were greatest at the same time. These phenomena were interpreted as indicating a decrease in the activity of the sympathetic nervous system with a relative preponderance of the parasympathetic during sleep and especially during the first two hours of sleep. As a result a decrease in the tonus of the muscle of the heart was assumed to occur at the same time as an increase in venous return, and hence in cardiac

4. Sahli, H.: Arch. f. exper. Path. u. Pharmakol. **19**:433, 1885.

5. Kraus, quoted by Luisada, A.: Arch. f. exper. Path. u. Pharmakol. **32**: 889, 1928.

6. Eppinger, H.; von Papp, L., and Schwarz, H.: Ueber das Asthma cardiale, Berlin, Julius Springer, 1924.

7. Katsch, G., and Pansdorf, H.: München. med. Wchnschr. **69**:1715, 1922.

output, because of peripheral vasodilatation. The consequence was pulmonary congestion and an attack of cardiac asthma, which, if severe enough, led to pulmonary edema.

The theory of Eppinger and his co-workers has been a subject of some controversy. Some writers appear to have accepted it; others have not. Thus Lauter [8] and Kroetz [9] reported low cardiac outputs in persons with cardiac dyspnea. There is considerable doubt as to the validity of most of the present respiratory methods for determining cardiac output in persons with congested lungs, and consequently this argument cannot be regarded as settled.

Insufficient Aeration.—Traube, the great German clinician, believed that paroxysmal dyspnea (as well as other forms of cardiac dyspnea) was due to congestion of the lungs, which caused the capillaries to encroach on the air spaces (*Lungenschwellung*) thereby interfering with the ventilation of the lungs and causing defective aeration of the blood.[10] This theory was modified by von Basch,[11] who thought that the decreased aeration was due to rigidity of the lungs (*Lungenstarre*) consequent on pulmonary congestion. However, Kraus [12] demonstrated not only that the ventilation was actually increased, but also that the alveolar carbon dioxide pressure was lower than normal in persons with cardiac failure. Hence, diminished ventilation of the lungs could not be the cause of the dyspnea.

Siebeck,[13] in 1912, demonstrated that the vital capacity was diminished and concluded that *Lungenstarre* did occur, but he found no alteration in the residual air and hence believed that *Lungenschwellung* did not take place to a significant degree. He thought that the dyspnea was caused by the rigidity of the pulmonary tissues, which caused uneven aeration with consequent increase in the carbon dioxide pressure of the arterial blood and respiratory stimulation. Porges,[14] on the other hand, confirmed Kraus' observation of abnormally low alveolar carbon dioxide pressure in persons with cardiac dyspnea. He believed that this was due to acidosis, which in turn was caused by inadequate oxygenation of the blood. Straub and Meier [15] found acidosis in some but not in all the patients they studied and concluded that cardiac dyspnea was due to a carbon dioxide acidosis.

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8. Lauter, S.: München. med. Wchnschr. **77**:593, 1930.
9. Kroetz, C.: Deutsches Arch. f. klin. Med. **164**:257, 1930
10. Traube, quoted by Eppinger,[6] p. 11.
11. von Basch, quoted by Eppinger,[6] p. 11.
12. Kraus, quoted by Eppinger,[6] p. 13.
13. Siebeck, R.: Deutsches Arch. f. klin. Med. **107**:252, 1912.
14. Porges, O., and Marconi, E.: Wien. klin. Wchnschr. **23**:454, 1910.
15. Straub, H., and Meier, K.: Deutsches Arch. f. klin. Med. **125**:477, 1918.

All these theories of diminished aeration of the arterial blood as the cause of cardiac dyspnea have been discredited in recent years by the work of Eppinger, von Papp and Schwarz,[6] Peters and Barr,[16] Eppinger, Kisch and Schwarz,[17] Fraser, Harris, Hilton and Linder,[18] Cullen, Harrison, Calhoun, Wilkins and Tims [19a] and Calhoun, Cullen, Harrison, Wilkins and Tims,[19b] to mention only a few of the authors who have applied modern methods to the problem. Their studies seem to be in general agreement in indicating that increased hydrogen ion concentration of the arterial blood is an exceptional finding in persons with cardiac dyspnea and occurs only in moribund patients or in patients with extreme degrees of pulmonary disease. In some instances the patients in the latter group may have carbon dioxide tensions of 60 or even 70 mm. of mercury, but such cases are rare, and usually the patients do not have paroxysmal dyspnea unless they also have bronchial asthma. Alkalosis, usually of mild degree, is on the other hand a common finding in patients with cardiac dyspnea (Fraser, Cullen, Calhoun and their co-workers).

Diminished Cardiac Output.—Most English and American investigators have concluded that the various forms of cardiac dyspnea are due to an accumulation of acid metabolites in the respiratory center dependent on a diminished cerebral flow of blood due to a decrease in the cardiac output. That this hypothesis is not correct was demonstrated in previous studies in the present series [19] in which it was shown that not only the arterial blood but blood obtained from the internal jugular veins of patients with dyspnea (nocturnal or produced by exertion) failed to show any of the postulated alterations in hydrogen ion concentration, carbon dioxide or oxygen content.

Nervous Cause.—Being dissatisfied with chemical theories of paroxysmal dyspnea, some authors have believed the syndrome to have its genesis in the nervous system. Hoffmann [20] went so far as to assume that paroxysmal dyspnea was a neurosis of the cardiac nerves. Brunn [21] believed the symptom to be due to a disturbance in water regulation leading to a passage of fluid from the tissues into the blood stream during the night in these patients, all of whom he believed to

16. Peters, J. P., and Barr, D. P.: J. Biol. Chem. **45**:537, 1921.

17. Eppinger, H.; Kisch, F., and Schwarz, H.: Das Versagen des Kreislaufes, Berlin, Julius Springer, 1927.

18. Fraser, F. R.; Harris, C. F.; Hilton, R., and Linder, G. C.: Quart. J. Med. **22**:1, 1928.

19. (*a*) Cullen, G. E.; Harrison, T. R.; Calhoun, J. A.; Wilkins, W. E., and Tims, M. M.: J. Clin. Investigation **10**:807, 1931. (*b*) Calhoun, J. A.; Cullen, G. E.; Harrison, T. R.; Wilkins, W. E., and Tims, M. M.: ibid. **10**:833, 1931.

20. Hoffmann, F. A., quoted by Eppinger,[6] p. 9.

21. Brunn, F.: Zentralbl. f. inn. Med. **49**:873, 1928.

have latent edema. This hydremic plethora was thought to be responsible for an increase in the degree of pulmonary congestion and for the consequent paroxysmal dyspnea. As evidence he cited the fact that diuretics may prevent attacks of paroxysmal dyspnea, and, further, that the attacks are often followed by the passage of large amounts of pale urine. The same mechanism was responsible, he believed, for the well known nocturia of cardiac failure. The beneficial action of morphine is, according to Brunn, to be ascribed to its action in holding the water in the tissues (Moliter and Pick [22]). In another article [23] Brunn showed that pituitary medication also tended to make the tissues retain water, and to this action, as well as to its effect on the central nervous system, he ascribed the beneficial effects of this drug in cases of paroxysmal cardiac dyspnea.

Gollwitzer-Meier [24] also believed that the seizures were due to nocturnal passage of water from the tissues into the blood stream. This led to pulmonary congestion (in persons with a strained left ventricle) which resulted in a decrease in the residual air which in turn caused reflex stimulation of breathing. This reflex was assumed but not demonstrated.

Brunn's hypothesis is attractive because it accounts for the fact that diuretic drugs, even if followed by only slight diuresis, may have a pronounced effect in preventing the attacks of dyspnea. However, the passage of fluid into the blood stream has not yet been demonstrated. If it did occur in significant amounts one would expect the hemoglobin concentration of the blood of such patients to be lower in the morning than in the evening. Actually, the reverse is true, as will be shown in the succeeding study in this series. The oxygen capacity is usually higher in the morning than in the evening, and this fact seems to us to constitute rather strong evidence against the validity of the "water shift" hypothesis.

Danzer [25] believed that an increase in the spinal fluid pressure during sleep might be a factor in the production of the attacks of dyspnea but offered no convincing evidence for his theory.

A number of authors believe that paroxysmal dyspnea is a reflex disturbance. The opinion of Eppinger, von Papp and Schwarz and of Gollwitzer-Meier, that reflexes from the lungs are responsible, has already been mentioned. Hess [26] believed the dyspnea to be due to a

22. Moliter, H., and Pick, E.: Arch. f. exper. Path. u. Pharmakol. **107**:185, 1925.

23. Brunn, F.: Ztschr. f. d. ges. exper. Med. **25**:176, 1921.

24. Gollwitzer-Meier, K.: Klin. Wchnschr. **10**:341, 1931.

25. Danzer, C. S.: Ann. Int. Med. **2**:239, 1928.

26. Hess, L.: Wien. Arch. f. inn. Med. **12**:477, 1926.

reflex effect on the pulmonary arteries from a myelomalacic heart. He supported his opinion by reports of pathologic conditions occurring in hearts, but not by conclusive experiments. Luisada [27] studied pulmonary edema produced in rabbits by the administration of epinephrine. He showed that drugs which stimulate the respiratory center increase the sensibility of these animals to pulmonary edema produced in this way, and that drugs which depress the brain have the opposite result. He also found that cutting the spinal cord in the cervical region prevented the development of pulmonary edema following the administration of epinephrine, and concluded that the effect of epinephrine was due not so much to the rise in blood pressure as to a reflex from the heart or aorta acting on a (hypothetic) center assumed to regulate the permeability of the pulmonary capillaries. Luisada's contribution contains an excellent review of the literature on the mechanism of the production of pulmonary edema.

Wassermann [28] described the cases of patients with angina pectoris and paroxysmal dyspnea, which he believed were due to a reflex from the root of the aorta, because relief was obtained by cutting the depressor nerves. Later,[29] he reported a rise in blood pressure and an increase in pulse rate occurring just before the attack of dyspnea. These signs led him to believe that the cause of the attacks was reflex stimulation of the central nervous system. He sought to produce an antagonistic reflex by pressure on the carotid sinus, a measure which was found beneficial in some instances. Wassermann concluded that paroxysmal dyspnea was a reflex from the aorta and that pulmonary edema was also due to a reflex of similar origin, causing narrowing of the pulmonary vessels.

Cheyne-Stokes Respiration.—Sir James Mackenzie [30] stated that the paroxysms of nocturnal dyspnea were to be attributed to Cheyne-Stokes respiration but offered no explanation for the cause of the latter phenomenon.

As a result of this summary of some of the more important contributions in the literature it may be stated that there seems to be general agreement that nocturnal dyspnea is in some way related to disturbed function of the cardiovascular system, but that the greatest diversity of opinion exists concerning the exact pathogenesis of this syndrome. We believed that any systematic investigation of the subject must begin with a clinical study. For the past four years we have carefully kept

27. Luisada, A.: Arch. f. exper. Path. u. Pharmakol. **32**:889, 1928.

28. Wassermann, S.: Wien. klin. Wchnschr. **37**:889, 1924.

29. Wassermann, S.: Wien. klin. Wchnschr. **40**:517, 1927.

30. Mackenzie, James: Diseases of the Heart, ed. 4, New York, Oxford University Press, 1925, p. 33.

records of patients' statements in regard to their dyspnea. The earlier records are of relatively little value because we did not at first know what questions to ask. However, our last thirty patients with nocturnal dyspnea have been exhaustively questioned, and the data of the present paper were obtained from their records. These data are based on the patients' statements in regard to their respiratory distress and, being subjective, are open to all the sources of error inherent in such studies. However, before we could make investigations by more exact methods it was necessary to have a starting point. The subjective aspects of the syndrome seemed to be a logical point of departure for the objective investigations to be reported later.

CLINICAL OBSERVATIONS

Of the thirty patients, three were observed in private practice and the remainder in the clinic for cardiac diseases and in the medical wards of the Vanderbilt University Hospital. Thirteen of the patients were ambulatory, and seventeen were observed while being treated in the hospital. The data in regard to the latter persons are somewhat more full because of the greater opportunity for clinical observations.

Race and Sex.—The series consisted of eleven white men, four white women, eight Negro men and seven Negro women, a total of fifteen white and fifteen Negro patients.

Age.—The oldest patient in the series was 68 years of age; the youngest was 23. The distribution by decades was as follows: between the ages of 20 and 30, three cases; between 30 and 40, two cases; between 40 and 50, twelve cases; between 50 and 60, seven cases, and between 60 and 70, six cases.

Chief Etiologic Factors.—In a number of patients more than one underlying cause of heart disease was present, and such persons have been classified according to which of these seemed to be most important. Accordingly, hypertension was considered as the chief etiologic disorder in fourteen cases; syphilitic aortic insufficiency in six; arteriosclerosis in five, and a rheumatic condition in two. The two last mentioned had mitral stenosis, and one of them had aortic insufficiency as well. In three patients none of the common causes of heart disease was present, and the conditions in these patients were classified under the term "cardiac hypertrophy, cause unknown." Three patients, in addition to having definite organic cardiac disease, presented all the signs and symptoms of cardiac neurosis. All of these were white female patients. One of them had the only case of uncomplicated mitral stenosis in the series. Her seizures of dyspnea occurred only in association with excitement, emotion, unpleasant dreams and "nervousness," and it seems probable that they were related to her cardiac neurosis rather

than to her organic cardiac disease. If this patient is excluded from the series, there remains no case of uncomplicated mitral stenosis in the group.

A number of authors have referred to paroxysmal dyspnea as a symptom of syphilitic aortitis in its earliest stage. There was no patient with that condition in this series, every patient with syphilitic aortitis having associated aortic insufficiency, hypertension or arteriosclerosis as a cause of dyspnea. In this clinic many cases of syphilitic aortitis are observed, and our experience indicates that this disorder in its uncomplicated form practically never causes paroxysmal dyspnea.

Eight patients in the series had angina pectoris, but only four of them had ever had the pain and the dyspnea simultaneously, and even these subjects had had many attacks of dyspnea without pain, and vice versa. It is therefore unlikely that any causal relationship exists between these two symptoms.

Objective Findings.—Aside from the characteristic clinical phenomena associated with the underlying disease, the patients with nocturnal dyspnea have regularly shown two signs, i. e., demonstrable cardiac enlargement and diminution in vital capacity. The majority of the patients had obviously enlarged hearts, but in a few obese patients, in whom the physical signs left one in doubt, teleroentgenograms have demonstrated an abnormally wide cardiac shadow. The vital capacity was not measured in three subjects, but the remaining twenty-seven exhibited a diminution of this function when compared to the normal standards of Peabody and Wentworth.[31] Gallop rhythm was noted in eight of the thirty subjects. Four patients had auricular fibrillation, and twenty exhibited premature beats. Cheyne-Stokes respiration was present in one half of the cases and will be discussed later.

Duration of Symptoms.—Every patient gave a history of more or less respiratory distress on muscular effort, but the duration of this symptom was variable. The longest duration was ten years, the shortest, one month, and the average, three and one-tenth years. Each of the patients had nocturnal dyspnea which varied in duration from five years to one month, the average being two and one-tenth years.

Edema had been present at one time or another in twenty-three of the thirty cases. The average period after edema was first noted was approximately one and one-half years. As a rule it was a late symptom, and in only three cases did edema develop prior to the onset of nocturnal dyspnea.

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31. Peabody, F. W., and Wentworth, J. A.: Clinical Studies on Respiration: V. The Vital Capacity of the Lungs and Its Relation to Dyspnea, Arch. Int. Med. **20**:443 (Sept.) 1917.

Predisposing and Precipitating Factors.—From what has been stated it appears that paroxysmal dyspnea is associated with disorders that cause a strain on the left side of the heart and more particularly with those that cause an initial strain on the left ventricle. In addition, however, there are a number of conditions which appear to bring on the seizures, and concerning these our patients have been questioned in considerable detail.

Position of the Body: Twenty-seven of the thirty patients stated that they were more short of breath in the recumbent than in the sitting posture. The remaining three patients who did not have orthopnea had paroxysmal dyspnea for two months or less and were the earliest subjects of the series. Three patients stated that they were more comfortable standing than sitting, but the majority agreed that the most favorable position was sitting on the side of the bed with their feet resting in a chair.

Blumgart and Ernstene pointed out the fact that the position of the patient's head may affect his dyspnea. Eleven of our patients preferred to have the head flexed.

Cough: This was an extremely frequent symptom. Seven patients said that their attacks were invariably precipitated by coughing, and that they never had attacks except following coughing. Sixteen additional persons stated that some of their attacks were precipitated by coughing but that they also had seizures which did not follow coughing. Seven patients stated that their attacks bore no relation to coughing. Expectoration of sputum tended to relieve the attack in fifteen of the twenty-three patients who had noted cough as a factor in the production of their seizures.

Activity: An important predisposing factor in many patients was the amount of activity indulged in during the day. Twenty-one patients had noted that they were more likely to suffer from nocturnal dyspnea following a day of activity than they were after they had been relatively quiet during the day. On the other hand, nine patients insisted that they were just as likely to have seizures after a day of rest as after a day of moderate activity.

Abdominal Distention: Seventeen patients observed that they were especially likely to be dyspneic when they suffered from distention, and these patients stated that either belching or the passing of flatus often relieved their seizures.

Size of the Preceding Meal: Twelve patients noted that a large evening meal appeared to be a predisposing cause of their attacks, which could be prevented or ameliorated by omission of the evening meal.

Bowel Movements: Twelve patients had noticed that they were more apt to have dyspneic seizures when they were constipated, and

that their breathing seemed easier following bowel movements. In these persons the dyspnea was not simply related to straining at stool; they all stated that their dyspnea began when they first noticed the desire for a bowel movement, tended to become worse the longer the defecation was postponed and disappeared within a short time following emptying of the rectum.

Hunger: One patient stated that nearly all his attacks occurred when he was hungry. He frequently asked for milk and a cracker and usually seemed to have less dyspnea following ingestion of that food. (Determinations of blood sugar made during his seizures revealed no hypoglycemia.) Seven other patients reported that they were likely to have seizures during hunger, and that the eating of a small amount of food often made them feel better, whereas the eating of large meals made the attacks worse.

Dreams: Several authors have pointed out that unpleasant dreams tend to cause seizures of paroxysmal dyspnea in certain patients, and this appeared to be the case in eight of our thirty cases. Three of these eight patients were white women who, in addition to having organic cardiac disease, were definitely psychoneurotic. However, the other five persons displayed no undue anxiety and had none of the usual signs of neurosis. Two of the patients had no nocturnal seizures at all except following nightmares or unpleasant dreams, whereas in the remaining six dreams were only one of several precipitating factors.

Temperature: For a number of years we have noticed that at the onset of unusually hot weather patients coming to the clinic for cardiac diseases are likely to complain of nocturnal dyspnea. In the present series, eight persons stated that heat was an important predisposing or precipitating factor in their attacks, and one of them stated that the warmth of the bed clothes appeared to cause seizures. The first attack in two patients occurred during very hot weather, and both of them have continued to have seizures whenever the room in which they sleep is unusually warm.

Urination: Seven patients complained of noticing dyspnea when they wanted to empty the bladder, and in two of them we had occasion to make objective studies concerning the breathing at such periods. The results, which will be published in a subsequent article, indicated clearly that dyspnea was aggravated by the desire to urinate and was relieved immediately following micturition.

Time of Onset of the Attacks.—The patients were questioned carefully in regard to the exact hour at which they noticed respiratory distress and as regards the relation of the attacks to the waking and sleeping states. Ten patients, most of whom had relatively mild dyspnea, stated that they never suffered from respiratory distress as long as they

were awake, at rest and in the upright position. They did, however, suffer from seizures during sleep. Twenty patients who had somewhat more severe dyspnea stated that they sometimes suffered from respiratory discomfort during their waking hours, even though they were at rest and in the sitting position. Of this group, one patient who had severe attacks of coughing each morning on awakening stated that the dyspnea was always worse in the morning when he coughed than in the evening, and two persons noticed no difference in the dyspnea during different parts of the day. However, the remaining seventeen subjects agreed that the dyspnea, when it occurred at all during their waking hours, was always more severe in the late afternoon—especially in the evening—than it was in the morning. They also stated that even though they remained in bed and in the same position throughout their waking period, their distress would still be worse toward the latter part of the day. Objective studies, which will be reported in the succeeding paper, were made in the patients who were in the hospital, and their statements were confirmed. It appears, therefore, that something occurs during the day which in many patients tends to produce dyspnea as night draws on. During the morning a patient may be entirely comfortable so long as he remains propped upright and at rest. At about 4 or 5 o'clock in the afternoon he is likely to notice a little discomfort, and by 8 or 9 o'clock he may have fairly severe respiratory distress. It should be noted that this type of dyspnea is nocturnal but not paroxysmal.

All of the thirty patients complained of attacks of shortness of breath which awakened them from sleep. Twenty stated that they frequently had seizures occurring immediately at the onset of sleep. Although relatively or entirely free from dyspnea on first settling themselves for the night, they would awake suddenly, just as they began to "doze off" to sleep, with a seizure of respiratory distress. Following a few minutes or seconds of discomfort they would become relieved and would again become somnolent only to experience another attack just as they passed into the sleeping state. Of these twenty patients, eight had no attacks except those of the nature described, whereas twelve also complained of seizures which awakened them from sound sleep after they had been sleeping for one or more hours. The latter attacks were often described as being of longer duration and more severe.

It is of interest to note that Cheyne-Stokes respiration was found in fifteen of the twenty patients who had seizures of dyspnea occurring at the onset of sleep. In the remaining five who had dyspnea of this type, periodic breathing was not observed, but these were ambulatory and were not seen during attacks. It is possible that these patients also might have been found to have Cheyne-Stokes breathing if they

had been observed during their seizures of dyspnea. The frequency with which patients complaining of shortness of breath of this type have exhibited Cheyne-Stokes respiration has made us wonder whether or not the subjective respiratory distress could be related in some way to their periodic breathing. Objective observations concerning this question will be presented in a later contribution.

Ten patients in the series of thirty stated that their seizures never came at the onset of sleep but always appeared after they had slept soundly for one hour or more. None of these patients had been found to have Cheyne-Stokes respiration. As has been stated, there were twelve persons who had seizures both at the onset of sleep and later on after sleep had lasted for an hour or more.

Attacks of acute pulmonary edema have been observed in six of the thirty patients. All these attacks have appeared after the subject had been asleep for some time, and no attack has occurred at the onset of sleep. Furthermore, no patient whose dyspneic seizures were limited in their occurrence to the onset of sleep has had an attack of acute pulmonary edema.

It is of interest to consider the ages of the patients in respect to the type of dyspnea experienced. The average age of the eight patients who had paroxysmal dyspnea only at the onset of sleep was 55 years, the youngest being 43 and the oldest, 68. These figures are in contrast to those for the ten subjects who had attacks which awakened them from sound sleep. Their average age was 42, the range being from 23 to 54. The twelve subjects who had attacks of both types were, as might be expected, intermediate in this respect, the average age being 50 years and the range of ages from 39 to 66.

SUMMARY

A clinical study has been made of thirty patients who had cardiac disease and who suffered from attacks of nocturnal dyspnea. Most of the subjects were more than 40 years of age. The chief causes of cardiac disease in these cases were hypertension, arteriosclerosis, and syphilitic aortic insufficiency. There were only two patients with rheumatic heart disease, and of these, only one had uncomplicated mitral stenosis. The occurrence of nocturnal dyspnea is restricted almost entirely to patients with disorders which cause a strain on the left ventricle. Uncomplicated syphilitic aortitis (i. e., without aortic insufficiency, occlusion of the coronary vessels or aneurysm) practically never causes nocturnal dyspnea.

Cardiac enlargement and diminished vital capacity were constant objective findings; premature beats and gallop rhythm occurred in a large number of the patients. Only four patients in the series had auricular fibrillation.

The following factors have been found to be precipitating and predisposing causes of the attacks: (1) the position of the body in twenty-seven cases, (2) cough in twenty-three cases, (3) the amount of activity engaged in during the preceding day in twenty-one cases, (4) abdominal distention in seventeen cases, (5) large evening meals in twelve cases, (6) constipation and the desire for bowel movement in twelve cases, (7) hunger in eight cases, (8) unpleasant dreams in eight cases, (9) heat in eight cases and (10) urination in seven cases.

Analysis of the histories of the cases indicates that nocturnal dyspnea may be subdivided into several types of respiratory distress:

1. A type which is not paroxysmal but which develops gradually during the course of the day, usually appearing first in the late afternoon and reaching its maximum intensity at bedtime. For this syndrome the name "evening dyspnea" is proposed.

2. Attacks of shortness of breath appearing only at the onset of sleep and tending to prevent the patient from reaching a state of deep sleep. However, if such a patient falls into a sound sleep he is likely to remain free from attacks throughout the remainder of the night. Patients with this type of dyspnea frequently exhibit Cheyne-Stokes respiration and are unlikely to have seizures of acute pulmonary edema.

3. Attacks of dyspnea which begin after the patient has begun to sleep soundly and which are likely to cause acute edema of the lungs. Cheyne-Stokes respiration is an infrequent finding in patients with this type of dyspnea.

4. Combination forms. The same patient may have all three types of dyspnea, or any two of them.

In subsequent articles objective observations will be presented concerning these various forms of respiratory distress.

THE DIFFERENCE IN CREATINE CONCENTRATION OF THE LEFT AND RIGHT VENTRICULAR CARDIAC MUSCLES

DAVID P. SEECOF, M.D.
NEW YORK
AND
CHARLES R. LINEGAR, A.B.
AND
VICTOR C. MYERS, PH.D., D.Sc.
CLEVELAND

Although the function of creatine in muscle has not been entirely elucidated, recent studies indicate that in the form of phosphocreatine it plays a vital rôle in muscular contraction. Data on the creatine content of the heart, the body's most active muscle, should possess considerable significance. When one of us (D. P. S.) was approached with regard to collaborating on a study of the creatine content of the heart, an idea formulated during the progress of pathologic studies, namely, that the left and right ventricles were qualitatively different muscles, led to the decision to make separate determinations on the two ventricles.

The idea that the ventricles may be different originated about ten years ago, during a review of the available data on the congenital anomalies of the heart which result from defects of development of the bulbus cordis. As summarized by Keith,[1] the data disclosed that the conus of the right ventricle was embryologically different from other portions of the heart.

Anatomic evidence that the two ventricles might be different was found in the works of MacCallum,[2] Mall [3] and others, whose careful

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Preliminary report read before the Experimental Medicine Section of the Cleveland Academy of Medicine, Jan. 8, 1932.

Presented in abstract at the annual meeting of the American Society of Biological Chemists, Cincinnati, April 10, 1933.

From the Department of Pathology, Cleveland City Hospital, and the departments of Pathology and Biochemistry of the Western Reserve University.

The chemical data in this paper are taken from a dissertation being submitted by Charles R. Linegar to the Graduate School of Western Reserve University in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

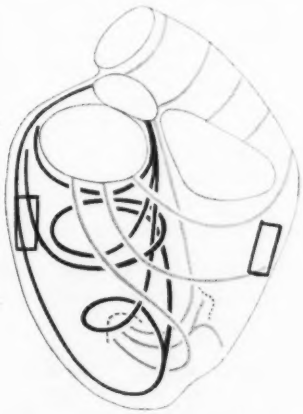
1. Keith, A.: Fate of the Bulbus Cordis in the Human Heart, Lancet **2**:1267, 1924.

2. MacCallum, J. B.: On the Muscular Architecture and Growth of the Ventricles of the Heart, Johns Hopkins Hosp. Rep. **9**:307, 1900.

3. Mall, F. P.: On the Muscular Architecture of the Ventricles of the Human Heart, Am. J. Anat. **11**:211, 1910-1911.

dissections revealed that the heart was not a single muscle, but was made up of overlapping and intertwining bundles, the chief of which were fairly separate and distinct for each of the two ventricles, as shown in the illustration.

Observations regarding differences between the left and right ventricles in relation to hypertrophy, dilatation, inflammations and degenerations made clinically and at autopsy suggested that these might not be due to the inequality merely in volume or quantity of the muscle of the respective ventricles, but that they could better be explained on qualitative differences between the muscles of the ventricles, differences such as are found between the various types of muscle in the same body.



Reproduction (from Mall [3]) showing schematically the course of the chief muscle bundles of the heart. The regions marked out are the locations at which the specimens were taken for the standard creatine determinations.

Finally, in unpublished histologic and cytologic studies it was found that in the hearts of the common laboratory animals the left ventricle contained larger amounts of glycogen and of mitochondrial substance than the right.[4]

The histologic studies revealed chemical differences between the two ventricles as pertains to glycogen and lipids. At this time the observations establish further chemical differences between the two ventricles, namely, the left ventricle has a higher concentration of creatine than the right.

The chemical studies to be recorded, therefore, in addition to furnishing data on the distribution of creatine in the muscles of the heart, also serve to demonstrate differences between the two ventricles.

4. Seecof, D. P.: Unpublished observations.

MATERIAL

The observations are based on 114 human and 9 animal hearts. The material used in correlated studies is given under the respective headings. The human hearts were obtained at autopsy from patients varying in age from birth to 83 years who died of various diseases. The animal hearts were obtained at the abattoir.

The ventricular samples for the chief analyses were taken from identical locations in each heart. These sites were chosen because they represented, as far as can be practically determined, the regions where, according to McCallum and Mall, the chief muscle bundles of the two ventricles are separate (illustration). In several instances other regions of the heart were taken to determine if the sites chosen were correct.

The samples were carefully trimmed of the epicardial fat and fibrous tissue, musculi carneae and endocardium.

The determinations on voluntary muscle were made, with few exceptions, on the pectoralis major of the same subject. For some studies, rabbit muscle was used.

METHOD

A. Actual.—The method employed in this work is a modification of that of Rose, Helmer and Chanutin.[5]

Procedure: Approximately 1 Gm. of cardiac (same procedure for voluntary and other muscle) muscle, stripped of visible fat, blood vessels, fibrous tissue, endocardium and epicardium is dropped into a previously weighed, glass-stoppered 100 cc. Erlenmeyer flask containing 20 cc. of double normal sulphuric acid. After the flasks are weighed, they are placed in the autoclave for forty-five minutes at 15 pounds' pressure. The flasks are then removed from the autoclave, twirled to break up the partially disintegrated fragments of muscle, and placed in the ice-box until the contents of the flasks are cooled to about 3 to 5 C. Now the contents of each flask are transferred to a 100 cc. volumetric flask with the aid of from 40 to 50 cc. of cooled distilled water and treated with 20 cc. of double normal sodium hydroxide which will bring the solution sufficiently close to room temperature. The reaction of the solution at this time should be faintly acid to either congo or methyl red. After the contents of each volumetric flask are diluted to volume, they are poured into a 250 cc. Erlenmeyer flask containing (exactly) 100 cc. of purified and saturated solution of trinitrophenol and mixed thoroughly. As soon as the precipitate has become flocculent, the half-saturated solution of trinitrophenol is filtered.

For the colorimetric determination, 2 cc. of 10 per cent sodium hydroxide is added to 20 cc. of this filtrate. After it is mixed, the solution is allowed to stand for ten minutes in order to develop the color completely, and a reading is made within fifteen minutes against a standard solution similarly prepared. (It is convenient to place these solutions against a white background in a porcelain pan so that the unknown solutions can be segregated with their corresponding standard solution before the readings are made.) Instead of using a curve for the colorimetric estimation, four standards were made up in half-saturated solution of trinitrophenol to contain 0.1, 0.15, 0.2 and 0.3 mg. of creatinine (of determined purity) per twenty cubic centimeters, respectively. If 1 Gm. samples are taken, these standards cover a range of from 116 to 348 mg. of creatine per hundred

5. Rose, W. C.; Helmer, O. M., and Chanutin, A.: A Modified Method for the Estimation of Total Creatinine in Small Amounts of Tissue, J. Biol. Chem. **75**:543, 1927.

grams of cardiac muscle. For extremely low creatine values or in instances when it was impossible to obtain 1 Gm. of stripped muscle from the right ventricle, two other standard solutions were employed. These two standards contained 0.05 and 0.075 mg. per twenty cubic centimeters, respectively.

Calculation:

$$\frac{S}{R} \times S_1 \times \frac{200}{20} \times \frac{100}{W} \times \text{factor} = \text{mg. of creatine per hundred grams of muscle.}$$

S = standard setting in mm.
R = unknown reading in mm.
S_1 = strength of standard, i. e., mg. of creatinine per twenty centimeters
W = weight of specimen
Factor = 1.16

TABLE 1.—*Error of Methods in Determining Creatine Content of Muscle*

Method of Protein Precipitation	Source	Number of Experiments	Number of Samples	Range		Variation, per Cent
				Low, Mg.	High, Mg.	
Tungstic acid	Rabbit voluntary muscle	3	5	530	557	5.1
			5	518	537	3.7
			3	528	539	2.1
	Human heart muscle	3	4	180	191	6.1
			2	138	146	5.8
			2	197	202	2.5
Trinitrophenol	Human heart muscle	6	4	229	241	5.2
			4	215	226	5.1
			4	158	164	3.8
			4	266	275	3.4
			3	172	176	2.3
			3	173	176	1.7
	Human voluntary muscle	2	3	390	409	4.9
			2	384	395	2.9

B. Experimental Error.—Preliminary determinations were carried out, the tungstic acid precipitation method of Rose, Helmer and Chanutin[5] being used. Although very satisfactory for rabbit voluntary muscle, this method did not apply so well to cardiac muscle because some of the tungstic acid filtrates were not entirely freed from a tinge of the color present in the autoclave specimens. It was found that saturation with dry trinitrophenol gave more satisfatory precipitation. Later half-saturated trinitrophenol was used because it was more expeditious. The values obtained by this modified procedure agreed closely with those of the tungstic acid method in the few comparisons made on rabbit voluntary muscle.

In order to evaluate the experimental error, several adjacent samples of muscle were analyzed simultaneously. Table 1 shows that the per cent variation with such checks on human cardiac muscle ranged from 1.7 to 5.2 per cent (average 3.5 per cent) and from 2.9 to 4.9 per cent for human voluntary muscle. In addition, samples ranging in weight from 0.4 to 3 Gm. and analyzed similarly gave figures within this range of experimental variation.

C. Recovery Experiments.—In the recovery experiments shown in table 2, creatine or creatinine in varying concentrations was added to muscle and the whole analyzed for total creatine (plus creatinine). In order to estimate the total creatinine in each sample, adjacent duplicates were analyzed and the two creatine values

averaged. Then by adding this averaged figure and the known addition, the total creatine value was obtained. The $\frac{\text{estimated value}}{\text{analytical value}}$ constituted the per cent of recovery. The per cent of recovery for this method ranged from 95.9 to 98.7 per cent on human cardiac muscle and from 94.3 to 103.7 per cent for the tungstic acid procedure. This establishes the maximum experimental error at about 5 per cent.

Further confirmation of the values in the experimental data is offered by the range of from 517 to 556 mg. creatine per hundred grams of muscle obtained for rabbit voluntary muscle, which is in close agreement with the observations of Dorner,[6] Mellanby,[7] Myers and Fine,[8] Bauman,[9] Riesser[10] and Palladin and Wallenburger.[11]

D. Samples of Different Locations.—In order to check the fact that the sites chosen for examination were correct, different portions of each ventricle, the inter-

TABLE 2.—*Recovery After Addition of Known Amounts of Creatine and Creatinine (in mg. per Gram)*

Method of Precipitation	Source	Calculated Creatine Content, Mg.	Addition as Creatine, Mg.	Total Creatine, Mg.	Creatine Found, Mg.	Per Cent Recovery	Deviation from 100%
Tungstic acid	Rabbit voluntary muscle	7.06	3.00	10.06	10.01	99.5	—0.5
		10.08	3.00	13.08	12.54	95.9	—4.1
	Human right ventricle	1.01	0.46	1.47	1.50	102.0	+2.0
Trinitrophenol	Human left ventricle	1.94	0.46	2.40	2.38	99.2	—0.8
		2.36	0.46	2.82	2.81	99.6	—0.4
		1.04	2.09	3.13	2.95	94.3	—5.7
		2.01	2.09	4.10	4.25	103.7	+3.7
	Human left ventricle	1.79	2.00	3.79	3.71	97.9	—2.1
		1.88	2.00	3.88	3.72	95.9	—4.1
		1.95	3.48	5.43	5.33	98.2	—1.8
		2.03	3.48	5.51	5.43	98.7	—1.3

ventricular septum and the musculi carneae were examined separately. In two experiments it was found that the septum gave figures 7 per cent lower, and the right ventricle figures 23 per cent lower, than the standard specimen of the left ventricle, showing that in creatine content the septum was intermediate between the left and the right ventricles. Different regions of the same ventricle in four experiments showed differences up to 6 per cent for the left ventricle and up to

6. Dorner, G.: Zur Bildung von Kreatin und Kreatinin im Organismus, besonders der Kaninchen, Ztschr. f. physiol. Chem. **52**:225, 1907.

7. Mellanby, E.: Creatin and Creatinin, J. Physiol. **36**:447, 1908.

8. Myers, V. C., and Fine, M. S.: The Creatine Content of Muscle Under Normal Conditions: Its Relation to the Urinary Creatinine, J. Biol. Chem. **14**:9, 1913.

9. Bauman, L.: The Determination of Creatine in Muscle, J. Biol. Chem. **17**: 15, 1914.

10. Riesser, O.: Weitere Beiträge zur Frage der Kreatinbildung aus Cholin und Betain, Ztschr. f. physiol. Chem. **90**:221, 1914.

11. Palladin, A., and Wallenburger, L.: Contribution à l'étude de la formation de la créatine dans l'organisme animal, Compt, rend. Soc. de biol. **78**:111, 1915.

24 per cent for the right as compared with the standard specimens of the respective ventricles. In three experiments the musculi carneae of the left ventricle showed 31 per cent less, and the musculi carneae of the right showed 22 per cent less, than the standard specimens of the respective ventricles.

OBSERVATIONS

A. Control Data.—I. Analysis of Dried Material: Cardiac muscle dried to constant weight at 60 C. gave from 90 to 116 per cent of the fresh weight values, and when dried at 104 C. gave from 18 to 82 per cent of the fresh weight values. Cardiac muscle, therefore, behaved similarly to other muscle in that it was not feasible to dry it before

TABLE 3.—*Percentage Difference Between Left and Right Ventricles in Relation to Variation in Solid Content* *

No. of Cases	Source	Range	Solid†		Ventricle				Absolute Difference, Left—Right	
					Left		Right			
			Left Ventricle, per Cent	Right Ventricle, per Cent	Wet, Mg.	Dry, Mg.	Wet, Mg.	Dry, Mg.	Wet, per Cent	Dry, per Cent
30	Human heart	Minimum	19.7	16.8	128	516	93	460	12.6	2.1
		Maximum	24.8	23.8	348	1,568	196	1,127	54.6	57.7
		Average	21.9	20.0	195	890	133	669	31.1	24.8
9	Animal heart	Minimum	20.5	19.8	245	1,075	208	941	8.6	6.0
		Maximum	24.5	23.6	379	1,745	328	1,547	21.9	19.9
		Average	22.4	21.8	308	1,385	265	1,226	14.0	11.5

* Dried to constant weight at 60 C. Dry values calculated (mg. per hundred grams of dry weight).

† The solid content of the right ventricle was higher than in the left in only one case (human): left ventricle, 22.2 per cent; right ventricle (fibrous), 23.8 per cent.

analysis. The values obtained at 60 C. were less variable, and this temperature was used for the determinations of the solid content.

Table 3 shows that the left ventricle had the higher solid content, and that the average individual difference between the left and the right ventricles in per cent of solid was higher in the human than in the animal hearts. In order to establish the difference in creatine in the two ventricles on a dry basis, the dry weight values were calculated from the fresh content by the equation: $\frac{\text{fresh weight creatine}}{\text{per cent of solid} \times 100} = \text{mg. of}$ creatine per hundred grams of dry muscle. The difference in 30 human hearts, when placed on a dry basis, decreased from 31.1 to 24.8 per cent, while the decrease in 9 animal hearts was from 14 to 11.5 per cent. The per cent of difference between left and right ventricles when calculated in "dry" weight remained sufficiently high for one to assert that the final differences were due only in small part to the variations in the water content of the two ventricles.

II. Autolysis and Postmortem Factors: The preliminary analyses made on 12 human hearts kept in the refrigerator at 4 C. for periods of from two to eight days following autopsy at once indicated that the

left ventricle had a higher creatine content than the right ventricle. In this series, the average creatine value for the left ventricle was 142 mg. and for the right 94 mg., giving an average difference of 34 per cent.

In order to determine the possible rôle of postmortem factors, autolysis, etc., 9 hearts were obtained from animals immediately on slaughter at the abattoir (table 4). In each of these hearts the creatine content of the left ventricle was higher than that of the right, and for the series the differences averaged 14 per cent. Moreover, as shown in table 5, the creatine content of 5 of these hearts was not greatly altered up to nine days in the refrigerator, in spite of the slight increase in the per cent of solid due to loss of water. In this connection it may be pointed out that the experiments of Myers and Fine,[12] Hoagland and McBryde,[13] Hammett,[14] Riesser,[15] and Hahn and Meyer [16] showed that antiseptic or

TABLE 4.—*Creatine Content of Left and Right Ventricles in Nine Animal Hearts*

Source	Left Ventricle, Mg.	Right Ventricle, Mg.	Average Combined Left and Right, Mg.	Difference Between Left and Right	
				Mg.	Per Cent
Beef	370	312	341	58	15.7
	379	328	354	51	13.5
	287	258	278	29	10.1
	280	249	265	31	11.1
	245	208	227	37	15.1
	266	243	255	23	8.6
Calf	335	294	315	41	12.4
	270	230	250	40	14.8
Lamb	342	267	305	75	21.9
Average	308	265	287	43	14.0

aseptic autolysis has no significant effect on the total creatinine (creatine plus creatinine) content of voluntary muscle, brain, liver, kidney and blood.

12. Myers, V. C., and Fine, M. S.: The Metabolism of Creatine and Creatinine: X. The Relationship Between Creatine and Creatinine in Autolyzing Tissue, J. Biol. Chem. **21**:583, 1915.

13. Hoagland, R., and McBryde, C. N.: Effect of Autolysis upon Muscle Creatine, J. Agric. Research **6**:535, 1916.

14. Hammett, F. S.: Creatinine and Creatine in Muscle Extracts: III. Concerning the Presence of Enzymes in Muscle Tissue Which Have Creatine and Creatinine as Their Substrates, J. Biol. Chem. **53**:323, 1922. V. A Comparison of the Rate of Creatinine Formation from Creatine in Extracts of Brain and Muscle Tissue, ibid. **59**:347, 1924.

15. Riesser, O.: Beiträge zur Physiologie des Kreatins, Ztschr. f. physiol. Chem. **120**:189, 1922.

16. Hahn, A., and Meyer, G.: Ueber die gegenseitige Umwandlung von Kreatin und Kreatinin: IV. Die Entstehung von Kreatinin im Organismus, Ztschr. f. Biol. **78**:91, 1923.

However, 2 human hearts kept in the refrigerator for three and four days following autopsy showed a marked decrease in creatine content. The three day samples showed a decrease of 8 per cent for the left ventricle and of 11 per cent for the right, while the four day samples showed a decrease of 27 per cent for the left and of 28 per cent for the right. In 3 human hearts left for three days in unsterilized containers

TABLE 5.—*Effect of Autolysis on Creatine Values (Average Figures)*

No. of Hearts	Source	Days	Per Cent Solid		Ventricle		Absolute Difference, Left—Right, per Cent
			Left Ventricle, per Cent	Right Ventricle, per Cent	Left Wet, Mg.	Right Wet, Mg.	
5	Animal heart	0	22.6	22.1	339	286	15.6
		2	....	....	340	...	....
		5	22.6	22.6	324	278	14.2
		9	22.7	23.0	325	271	16.6
1	Human heart	0	....	....	254	209	17.7
		3	....	....	233	165	26.0
1	Human heart	0	....	....	170	118	30.6
		4	....	....	124	85	31.4
3	Human* heart	0	....	....	150	107	28.6
		3	....	....	84	37	55.9

* Left in unsterilized containers at room temperature.

TABLE 6.—*Creatine Values in Relation to Postmortem Factors*

Hours Post Mortem	No. of Cases	Left Ventricle, Mg.	Right Ventricle, Mg.	Average Combined Left and Right, Mg.	Difference Between Left and Right	
					Mg.	Per Cent
1- 3	16	208.0	163.0	185.5	45.0	21.6
4- 12	37	215.8	151.4	183.6	64.4	29.8
13- 24	28	202.9	136.4	169.7	66.5	32.3
25- 36	4	212.3	143.0	177.7	69.3	32.6
37- 48	3	169.3	120.7	145.0	48.6	28.7
49- 96	11	168.7	108.7	138.7	61.0	35.6
97-120	3	203.0	125.3	164.2	77.7	38.2
1- 36	85	209.8	148.2	179.0	61.6	29.4
37-120	17	174.9	113.8	144.4	61.1	34.9

at room temperature the average figures showed a decrease of 44 per cent for the left ventricle and of 70 per cent for the right. The decrease was always greater in the right ventricle than in the left.

This variance in behavior between animal and human hearts might be explained on the basis that in man, bacterial action, especially in the right ventricle, may lead to a disappearance of the creatine (Hunter [17]).

Subsequent studies revealed that in the 102 cases shown in table 6 the averages of the creatine content of the ventricles did not change

17. Hunter, A.: Creatine and Creatinine, Monographs on Biochemistry, New York, Longmans, Green & Co., 1928.

TABLE 7.—*Creatine Content of Human Heart Muscle in 102 Cases*

Serial No.	Age, Years	Sex	Creatine Content of Heart				Heart Weight, Gm.	Creatine of Voluntary Muscle, Mg.	Post Mortem, Hours
			Left Ventricle, Mg.	Right Ventricle, Mg.	Difference Absolute, Mg.	Difference, per Cent			
18	60	M	369	283	86	23.3	500	520	10
115	60	F	348	158	190	54.6	450	564	15
92	46	M	321	176	145	45.2	400	446	8
71	¾	M	278	214	64	23.0	54	343	2½
91	47	M	276	176	100	36.2	375	...	2
99	67	F	275	152	123	44.7	350	308	3
110	22	F	271	176	95	35.0	225	442	11
117	6	M	269	149	120	44.6	75	321	6
39	68	F	265	212	53	20.0	450	456	1
45	78	M	263	150	113	43.0	475	472	15
96	29	M	263	200	63	24.0	175	...	20
25	64	M	259	189	70	26.0	200	...	7
78	44	M	255	151	104	40.8	325	487	8
94	45	M	255	179	76	29.8	300	...	7
105	54	M	254	209	45	17.7	300	437	2
24	29	M	247	181	66	26.7	400	427	5
76	78	M	246	153	93	37.8	425	431	12
79	50	M	246	151	95	36.8	300	379	15
69	58	M	242	157	85	35.1	275	412	34
19	15	M	239	142	97	40.6	200	...	17
36	46	M	237	204	33	13.9	350	428	2
59	43	M	236	196	40	16.9	250	...	7
93	3	M	234	147	87	37.2	100	...	13
111	47	M	233	173	60	25.8	350	397	4
112	44	M	232	164	68	29.3	250	417	6
81	65	M	231	169	62	26.8	375	458	10
21	53	F	231	150	81	35.0	200	...	6
48	29	F	230	195	35	15.2	175	...	7
43	61	M	227	130	97	42.7	300	483	15
41	44	M	226	158	68	30.1	500	452	12
98	83	F	225	142	83	36.9	300	347	19
88	60	F	223	155	68	30.5	350	382	36
23	46	M	222	170	52	23.4	400	433	14
103	33	M	220	144	76	34.5	250	433	16
106	30	F	219	134	85	38.8	325	301	7
28	38	F	219	171	48	21.9	500	319	4
72	67	F	219	107	112	51.1	400	368	15
89	39	M	218	123	95	43.6	600	392	120
74	1½	F	218	176	42	19.3	85	...	3
26	22	M	216	130	86	39.8	275	428	30
95	4	M	207	138	69	33.2	100	...	18
82	49	F	207	163	44	21.3	400	376	3
57	33	M	206	180	26	12.6	325	382	14
90	48	M	205	98	107	52.2	400	387	96
42	75	M	205	119	86	42.0	425	488	10
100	32	M	203	147	56	27.6	375	297	9
22	31	F	200	116	84	42.0	175	393	9
109	35	F	200	143	57	38.5	275	385	8
75	40	M	196	124	72	36.7	600	342	72
108	37	M	196	178	18	9.2	250	462	4
53	62	M	196	112	84	42.9	300	...	108
66	75	M	195	141	54	27.7	450	440	120
34	58	F	195	156	39	20.0	350	324	10
35	26	F	194	146	48	25.0	375	346	19
68	52	M	192	167	25	13.0	300	347	2
64	56	M	192	116	76	39.6	250	487	3
97	50	M	192	178	14	7.3	750	348	1
20	51	M	190	134	56	29.5	225	...	41
54	75	M	190	124	66	34.7	450	...	84
114	33	F	190	140	50	26.3	650	...	4
55	27	M	188	124	64	34.0	400	411	17
73	50	M	188	108	80	42.6	300	...	12
30	50	M	188	127	61	32.4	210	297	11
50	46	F	187	125	62	33.2	300	387	8
62	36	M	184	134	50	27.2	500	410	6
84	69	M	183	163	20	10.9	300	417	20
15	62	M	183	120	63	34.4	750	...	15
87	6	M	182	134	48	26.4	140	320	15
83	60	M	181	104	77	42.5	450	376	24
27	23	F	178	117	61	34.3	275	368	72
116	47	M	178	111	67	37.6	560	348	7
107	55	M	175	116	59	33.7	475	340	66
40	77	M	175	114	61	34.9	600	261	65
47	47	M	174	114	60	34.5	350	...	16
51	58	M	174	135	39	22.4	250	...	8
67	40	M	174	118	56	32.2	250	398	50

TABLE 7.—*Creatine Content of Human Heart Muscle in 102 Cases—Continued*

Serial No.	Age, Years	Sex	Creatine Content of Heart				Heart Weight, Gm.	Creatine of Voluntary Muscle, Mg.	Post Mortem, Hours
			Left Ventricle, Mg.	Right Ventricle, Mg.	Difference Absolute, Mg.	Difference, per Cent			
16	39	M	171	113	58	33.9	350	...	19
44	50	M	171	93	78	45.6	500	...	12
102	2 mo.	F	170	158	12	7.1	20	369*	3
113	60	M	170	118	52	30.6	500	364	20
32	23	M	170	120	50	29.4	275	310	11
101	61	M	170	106	64	37.6	350	398	16
63	56	M	169	102	67	39.6	500	452	48
70	42	M	168	130	38	22.6	300	330	32
85	54	M	165	98	67	40.6	350	327	72
52	36	M	163	134	29	17.8	300	427	3
17	77	M	163	127	36	22.1	375	...	3
86	76	M	162	153	9	5.6	400	397	20
58	55	M	160	100	60	37.5	350	418	24
65	58	M	160	124	36	22.5	450	...	4
29	43	F	158	120	38	24.1	275	282	12
31	68	M	152	144	8	5.3	500	339	20
49	50	M	149	126	23	15.4	475	393	48
104	56	M	148	117	31	20.9	925	275	72
60	60	F	146	109	37	25.3	825	...	14
46	46	M	145	112	33	22.8	400	...	22
77	N.B.	F	143	148	—5	—3.5	20	296	6
80	52	M	142	88	54	38.0	325	364	66
38	43	M	138	114	24	17.4	275	367	12
33	35	F	130	113	17	13.1	375	...	3
61	52	F	116	112	4	3.4	350	...	2
56	62	M	108	82	26	24.1	250	258	72

* Iliopsoas muscle.

significantly within thirty-six hours post mortem. Furthermore, although there was a decrease in the absolute values after thirty-six hours, the drop in the creatine content of the right ventricle appeared earlier and was greater than that of the left; therefore the difference between the values for the left and the right ventricles was practically unaltered.

However, in order that the factors mentioned might be excluded, only the 85 specimens which were examined within thirty-six hours post mortem were used in the summarizing tables.

B. Data on Ventricles.—Table 7 gives the findings on the creatine content of the left and the right ventricles (determined by the trinitrophenol precipitation method) in the series of 102 human hearts and also the other data used for the correlation tables. In every case except that of the new-born, the creatine concentration in the left ventricle was higher than that in the right. This case was omitted in the summarizing tables. In the correlation tables, the data on 17 hearts examined after thirty-six hours post mortem were omitted to eliminate the factors of autolysis and postmortem errors.

The distribution of the 84 hearts grouped according to 50 mg. variations of creatine values is shown in table 8. The absolute figures varied between 93 and 369 mg. for both ventricles. The left ventricle in 76 of 84 hearts showed a range of from 150 to 300 mg.; the right ventricle

in 77 gave a range of from 100 to 200 mg. The average combined creatine content of the left and the right ventricles showed that 82 gave creatine values between 100 and 250 mg.

In table 9, the data on 84 hearts are summarized according to range, mean and average values of creatine content of each ventricle. The

TABLE 8.—*Creatine Content of Left and Right Ventricular Heart Muscle*

Range, Mg. per 100 Gm.	Distribution in 84 Hearts		
	Left Ventricle	Right Ventricle	Average Combined Left and Right Ventricles
93– 99	0	1	0
100–149	5	44	21
150–199	33	33	42
200–249	31	5	19
250–299	12	1	1
300–349	2	0	1
350–369	1	0	0

TABLE 9.—*Creatine Content of Right and Left Ventricles in 84 Hearts**

	Left Ventricle	Right Ventricle
Range	116 to 369	93 to 283
Mean	243	188
Average	211	148

* Milligrams of creatine per hundred grams of wet muscle.

TABLE 10.—*Distribution of Cases According to Percentage Differences of Right and Left Ventricles*

Percentage Difference, Left and Right	Number of Hearts
3– 9	6
10–19	11
20–29	27
30–39	26
40–49	12
50–55	2

range for the left ventricle was from 116 to 369 mg. with an average of 211 mg., and the range for the right was from 93 to 283 mg. with an average of 148 mg.

Table 10 shows the distribution of creatine in 84 hearts according to percentage differences between the left and the right ventricles. The differences ranged from 3 to 55 per cent. Of the 84 hearts, 78 (or 93 per cent) gave differences of over 10 per cent, outside the range of experimental error.

Table 11 summarizes the absolute and percentage differences between the left and the right ventricles. The percentage differences

were calculated by using the left ventricles (with the higher figure) as the standard. The average difference between left and right ventricles was 63 mg., or 30 per cent.

The findings in the 9 animal hearts are given in table 4, which, summarized in table 12, shows the range of absolute values to be from 266 to 379 for the left ventricle, or an average of 308, and from 208

TABLE 11.—*Differences Between Creatine Content of Right and Left Ventricles*

	Absolute Difference, Mg. per 100 Gm.	Absolute Difference, per Cent
Range of 84 hearts	4 to 190	3 to 55
Mean	97	29
Average	63	30

TABLE 12.—*Creatine in Left and Right Ventricles of 9 Animal Hearts* *

	Left Ventricle, Mg.	Right Ventricle, Mg.	Difference Between Left and Right	
			Mg.	Per Cent
Range	266 to 379	208 to 328	23 to 75	8.6 to 21.9
Mean	322.5	268.0	49	15.3
Average	308.2	263.2	45	14.6

* Milligrams of creatine per hundred grams of fresh muscle.

TABLE 13.—*Relationship Between Age and Creatine Values in 85 Hearts*

Age Range	Number of Cases	Ventricle			Absolute Difference	
		Left, Mg.	Right, Mg.	Average Combined Left and Right, Mg.	Mg.	Per Cent
New-born	1	143	148	146	—5	—4
New-born to 1	2	224	186	205	38	17
1 to 15	6	225	148	186	77	34
16 to 30	9	221	156	189	65	29
31 to 50	35	203	146	175	57	28
51 to 70	26	212	148	180	65	30
71 to 83	6	211	141	176	70	33

to 328, or an average of 265 for the right ventricle. Table 12 also shows that the range of difference between left and right ventricles was from 23 to 75 mg., or from 8.6 to 21.9 per cent with an average of 43 mg., or 14 per cent.

C. Correlation Data.—On correlating the findings in the human hearts with other available data, it is found that in relation to age as shown in table 13 at birth there is little difference between the creatine content of the left and right ventricle, and that the values are decidedly lower than those obtained shortly after birth. Within the first year the figures for both ventricles reach a maximum. There is essentially

no change up to the thirty year period. In the age period from 30 to 50 there is a definite drop in the creatine content of both ventricles, but with further increasing age there is again an increase. It is further of interest that the difference rises during the growth period (from 1 to 15 years) to 34 per cent, falls in the age period from 30 to 50 to 28 per cent, but again rises with increasing age to 33 per cent.

Correlating the creatine content with heart weight, some very interesting findings are noted (table 14). In the infants with hearts of 50 Gm. or under the creatine content is low. The maximum values are found in hearts weighing from 50 to 150 Gm. During the increase of weight up to 250 Gm., i. e., growth hypertrophy, the actual values are practically unchanged, but there is a decrease in the percentage difference (from 37 to 29 per cent). A further increase in weight from 250 to 350 Gm., which may be regarded as a physiologic hypertrophy, shows

TABLE 14.—*Relationship Between Heart Weight and Creatine Content in 85 Hearts*

Heart Weight, Range	Number of Cases	Ventricle			Absolute Difference, Left—Right	
		Left, Mg.	Right, Mg.	Average Combined Left and Right, Mg.	Mg.	Per Cent
20 to 50	2	157	153	155	4	2
51 to 150	6	231	159	195	72	37
151 to 250	14	224	159	191	65	29
251 to 350	30	202	143	172	59	29
351 to 450	20	216	147	181	69	32
451 to 550	8	219	156	188	63	29
551+	5	178	132	155	46	26

some decrease in the absolute figures while the percentage difference remains constant. With hypertrophy from 350 to 450 Gm., there is a rise in both the absolute values of each ventricle and the percentage difference (from 29 to 32 per cent). With the beginning of a definite pathologic hypertrophy (weights above 450 Gm.), there is a slight increase in absolute values for both ventricles while the percentage difference falls (from 32 to 29 per cent). Beyond 550 Gm. the absolute values fall to figures found in early infancy, with a fall in the percentage difference (from 29 to 26 per cent).

The pectoralis major, because it was easily obtained at autopsy, was used as the voluntary muscle for comparing the creatine values of cardiac and voluntary muscles. Table 15 shows the findings in 60 cases. The voluntary muscle figure ranged from 258 to 564 mg., giving an average of 394 mg. All but 5 of the 60 gave values between 300 and 500 mg. The per cent of solid ranged from 21.5 to 27.9, an average of 24.4.

The observations of Myers and Fine [8] on the rabbit would lead one to believe that the creatine content of voluntary muscle in a given species

is relatively constant under normal conditions. How is one to account for the rather wide fluctuations encountered in the 60 human hearts recorded in table 15? The low figures might be accounted for by the fact that the patients had been in a state of cachexia for some time prior to death, and this appears to have been the case, but high values for the creatine content of the voluntary muscle are not so readily explained. It has been shown, however, that the creatine content of muscle may be raised by administration of creatine and creatinine. By intravenous injection of creatine in cats, Folin and Denis [18] produced a temporary increase of from 9.2 to 26.6 per cent (in 1 case, 70 per cent) in the creatine content of the voluntary muscle. Similarly, Myers and Fine [19] reported a less pronounced increase of about 5 per cent in rabbits on subcutaneous injection of creatine (and also creatinine). More recently Chanutin and Beard [20] were able to produce an increase of from 5 to

TABLE 15.—*Comparison of Creatine Content of Voluntary and Cardiac Muscle*

Number of Cases in Group	Voluntary Muscle		Ventricular Muscle		
	Range,* Mg.	Average, Mg.	Average Left, Mg.	Average Right, Mg.	Average Combined Left and Right, Mg.
10	282-321	305	202	140	171
10	324-364	344	194	151	173
10	367-393	380	201	136	168
10	397-427	410	200	146	173
10	427-452	436	248	165	199
10	456-504	488	255	167	209

* Average creatine value for voluntary muscle in the 60 cases was 394 mg. per hundred grams.

10 per cent in the creatine content of the muscle of the mouse by adding creatine to the diet. It is therefore possible to raise the creatine level of voluntary muscle by the administration of creatine and creatinine, and this fact would suggest that the retention of creatinine in renal disease should bring about an increase in the creatine content of both voluntary and cardiac muscle.

The 60 cases in table 15 have been arranged according to the magnitude of the creatine content of the voluntary muscle, and the averages

18. Folin, O., and Denis, W.: Protein Metabolism from the Standpoint of Blood and Tissue Analysis: III. Further Absorption Experiments with Especial Reference to the Behavior of Creatine and Creatinine and to the Formation of Urea, J. Biol. Chem. **12**:141, 1912. VII. An Interpretation of Creatine and Creatinine in Relation to Animal Metabolism, J. Biol. Chem. **17**:493, 1913-1914.

19. Myers, V. C., and Fine, M. S.: The Influence of the Administration of Creatine and Creatinine on the Creatine Content of Muscle, J. Biol. Chem. **16**:169, 1913.

20. Chanutin, A., and Beard, H. H.: A Study on the Effect of Feeding Creatine on Growth and Its Distribution in the Liver and Muscle of Normal Mice, J. Biol. Chem. **78**:167 (June) 1928.

are given for groups of 10. One may assume on the basis of data in the literature that the normal creatine content of voluntary muscle in man is close to 400 mg. It will be noted that the creatine content of the left ventricle remains fairly constant at close to 200 mg. in the first four groups, but that as soon as the creatine content of the voluntary muscle begins to rise above the assumed saturation point of about 400 mg. there is likewise a corresponding rise in the creatine content of the cardiac muscle. The cause of the relatively higher creatine values in the voluntary muscle in the last 20 of the 60 hearts is not entirely clear, but it is evident that renal insufficiency was the important factor in a number of them. In the last group of 10 hearts, 5 of the patients suffered from arteriolar nephrosclerosis, 3 from pneumonia, 1 from pyelitis and generalized arteriosclerosis and 1 from Banti's disease and emphysema. It might be further noted that the last 2 hearts in this group of 10 were the first two (nos. 18 and 115) mentioned in the general table 7, and had the highest content of creatine in the left ventricle and voluntary muscle of any of the specimens in the series. Both cases showed arteriolar nephrosclerosis and cardiac hypertrophy and dilatation at autopsy.

Unfortunately the determination of the blood creatinine was made in only 1 of these cases (no. 18) and was found to be 25.1 mg. One of us (V. C. M.) has repeatedly noted that in persons suffering from arteriolar nephrosclerosis the blood creatinine may be excessively high in proportion to the urea. Obviously, this marked retention of creatinine not only would raise the figure for the creatine in the muscle by the amount of the preformed creatinine, but would tend to shift the equilibrium between creatine and creatinine toward the creatine side, and thus raise the true values for creatine in the muscle as well. There would appear to be little doubt that this was the explanation for the very high creatine content of both voluntary and cardiac muscle in these 2 cases (nos. 18 and 115). This is a problem which we are studying further at the present time, and hope to discuss in another paper in the near future. We have considered this question here because of its possible bearing on our present problem, but it is quite clear that the difference between the right and the left ventricular muscles persists through all the fluctuations of the absolute values as shown in the table.

COMMENT

A. Significance of Findings.—It should be pointed out that our studies on the creatine of the individual ventricles were carried out independently, i. e., without any knowledge of prior work along these lines, and, as previously indicated, were undertaken not as isolated chemical investigations or for the correlations of the creatine values of the heart in association with other problems on creatine metabolism, but primarily for their value in regard to the concept that the left and right

ventricles were qualitatively different muscles. The data are of twofold significance. First, they reveal differences in the creatine content of the two ventricles of the heart; second, they serve to confirm the concept that the ventricular muscles are qualitatively different.

There are references pertaining to the creatine content of the "heart." These refer to the organ as a whole, or imply that the figures given are applicable to the "heart" when analyses were carried out on samples of the left ventricle only (Katz [21]), and in some the exact regions of the heart examined are not specified.

As far as we have been able to determine from a search of the literature (after our work was well under way) there are only two previous references to creatine determinations carried out separately on the different portions of the heart.

Constabel,[22] on examining 38 human hearts at autopsy (hours post mortem not specified), found a difference of 10 per cent between the left and the right ventricle to be general. In 2 hearts with left ventricular hypertrophy (due to aortic insufficiency), the differences were 20 per cent (160 left and 128 right) and 26 per cent (175 left and 130 right). Moreover, he could find no correlation between the creatine content of the heart and age and sex. He stated that he believes that when the heart action is good the creatine content is high, but when the action is weak, especially in fatty changes, the creatine content is low. (Since the absolute figures were never above 200 mg. per hundred cubic centimeters, we believe that he worked with hearts obtained many hours post mortem.)

Vollmer [23] determined the phosphoric acid and creatine content of five different portions of the heart and found for the ventricles averages of 221 mg. for the left and 173 mg. for the right, or a difference of 21 per cent. Moreover, he found that both the creatine and the phosphoric acid contents of the ventricles were higher than that of the auricles. Zondek, Kraus and Wolheim found differences in potassium and calcium between auricles and ventricles. Vollmer warned, however, against drawing physiologic deductions from these chemical differences, since the latter may be due to variations of the connective tissue, elastic fibers, fat content, vascular supply and innervation of the different portions of the heart. He also studied postmortem effects and stated that Riesser [15]

21. Katz, L. N.: The Asynchronism of Right and Left Ventricular Contractions and the Independent Variations in Their Duration, Am. J. Physiol. **72**:655, 1925.

22. Constabel, F.: Ueber den Kreatingehalt des menschlichen Herzmuskels bei verschiedenen Krankheitszuständen, Biochem. Ztschr. **122**:152, 1921.

23. Vollmer, H.: Untersuchungen über den Kreatin- und Phosphorsäuregehalt verschiedener Herzteile, Ztschr. f. d. ges. exper. Med. **65**:522, 1929.

found no significant change in creatine up to forty-eight hours; in his own experiments he found a drop of 5 per cent in twenty-four hours and 3 per cent in the next twenty-four hours, or 8 per cent for the entire forty-eight hours.

Our findings on the creatine differences of the two ventricles confirm and extend the findings of Constabel and Vollmer.

B. Significance of the Differences Between the Ventricles.—In a series of 85 human hearts examined within thirty-six hours post mortem the creatine content of the left ventricle was found to be greater than that of the right in all cases except 1 (in a new-born infant). For the series, the creatine content of the left ventricle averaged 30 per cent more than the right. In a series of 9 fresh animal (cattle) hearts, the left ventricle showed a higher creatine content than the right in every case, and for the series the content of the left ventricle averaged 14 per cent higher than that of the right. The smaller difference in the animals, if not due to variation of species, may well be due to the fact that there were no abnormal hearts, i. e., hearts with hypertrophied ventricles. Constabel [22] found the left ventricle to be 10 per cent higher in "normal" hearts and from 20 to 26 per cent higher in hypertrophied hearts. Vollmer found the left ventricle to be 21 per cent higher.

These differences are not as great as between the light and the dark muscle of birds, or between voluntary, cardiac and smooth muscle in a given animal, but they are of the same magnitude as exists among the different skeletal muscles in the same body (Riesser,[15] Ferdmann and Feinschmidt [24]). Vollmer [23] believed that the differences in creatine content of the two ventricles might not have any physiologic significance but might be due in part to variations of fatty, fibrous and elastic tissue, blood supply, innervation and water content. This view is not justified, since it is not only in creatine content but in other elements that the two ventricles differ. Differences in glycogen, lipids, phosphoric acid (Vollmer), inorganic salts, potassium and calcium have been recorded. Wearn [25] showed variations in the number of capillaries of different portions of the heart in man and in animals. There are electrocardiographic differences between the ventricles which may again indicate qualitative differences between the left and the right ventricles. And there are probably other differences with which we are not acquainted.

Moreover, it is conceivable that the differences in the very fatty, fibrous, elastic tissue, blood supply, innervation and water content, indicate that the two ventricles may be regarded as different muscles.

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24. Ferdmann, D., and Feinschmidt, O.: Zur Frage der Verteilung der Kreatinphosphorsäure in verschiedenen Muskeln und Organen des tierischen Organismus, Ztschr. f. physiol. Chem. **178**:173, 1928.

25. Wearn, J. T.: The Extent of the Capillary Bed of the Heart, J. Exper. Med. **47**:273, 1928.

The creatine contents of various muscles in the same animal and "comparable" muscles in different species of animals vary and probably in association with functional activities. Palladin and Ferdmann [26] showed in voluntary muscle under "training" an increase in creatine content of from 10 to 20 per cent.

The practical point is that the differences in creatine exist. It is beyond the scope of this communication to enter into a discussion or to review the available knowledge on creatine and its rôle in muscular activity. Excellent comprehensive reviews are those of Hunter,[17] Milroy,[27] and Myers.[28] It is now fairly well established that creatine, as phosphocreatine, plays an active rôle in muscular contraction.

While we were planning studies to obtain evidence that functional differences exist between the muscles of the two ventricles, Dr. Harold Feil called our attention to the fact that it was available in the works of Katz.[21] Having established, beyond any doubt, that there was an asynchronism between the two ventricles, Katz, by a brilliant analysis of his data, concluded that the asynchronism could not be accounted for, entirely, by merely physical factors such as differences in pressure, tension and volume in the ventricular chambers, but that some unknown factors were involved. Our analysis of his findings leads us to believe that the explanation for the asynchronism and the electrocardiographic findings lies in the fact that the two muscles are qualitatively different, and we venture to suggest that some of the irreconcilable variations of the asynchronism may be due to age factors which seem to modify the qualitative differences between the muscles of the two ventricles.

In this connection it is of interest to point out that from what is known regarding the relationship between creatine content and muscular contraction it could be predicted that since the left ventricle has a higher creatine content (light versus dark muscle) its contractions should be faster, more energetic, etc., and curiously enough the findings of Katz confirm this prediction.

It is possible that any factor which alters the creatine content of the heart may alter its action, and in view of the normally different creatine contents, the added variations may disturb anew the conditions prevailing. Moreover, as is known for the skeletal muscles in the "myopathies," since single groups of muscles are affected, it is conceivable that in the heart, one or the other of the chambers may be affected by different increases or decreases of creatine in various diseases. It is possible that

26. Palladin, A., and Ferdmann, D.: Ueber den Einfluss des Trainings auf den Kreatingehalt der Muskeln, Klin. Wchnschr. **6**:2386, 1927.

27. Milroy, T. H.: The Present Status of the Chemistry of Skeletal Muscular Contraction, Physiol. Rev. **11**:515 (Oct.) 1931.

28. Myers, V. C.: Creatine and Creatinine, Yale J. Biol. & Med. **4**:467 (March) 1932.

some of the cardiac (and other muscular) abnormalities seen in fevers, metabolic disturbances, etc., may be due to chemical alterations, especially if only one of the ventricles is affected.

The realization that the left and right ventricles (as well as other portions) of the heart are chemically different may have some value in pharmacologic and therapeutic measures as applied to the heart. It would be of interest to attempt to correlate the effects of various drugs acting on the heart with the chemical alterations these may invoke along the lines done for voluntary muscle by Masayama and Riesser.[29] It may be found beneficial to administer along with other cardiac stimulants in heart "failure," as in the myopathies, creatine or some of its precursors.

III. The New Concept: In summarizing his embryologic findings on the bulbus cordis, Keith, in 1924, stated: "My aim will be to demonstrate the parts of the ventricle formed out of this element and to show reason why separate consideration must be given to these parts in all our attempts to unravel the exact mechanism of the ventricular pump." To paraphrase Keith, we believe there is sufficient evidence at hand to state that separate consideration must be given to the right and left ventricles in all our attempts to unravel the exact mechanism of the ventricular pump.

The fact is that the heart is not a single muscle but is made up of separate bundles, each with attachments at the valvular orifices at the base and in the regions of the papillary muscles. One of us (D. P. S.) has undertaken studies on these individual bundles, but progress has been delayed by technical difficulties. It is hoped that the investigation will be completed in the near future. The preliminary findings indicate that it may be shown ultimately that there are differences between these individual muscle bundles. Just as there occur degenerations, inflammations and hypertrophies of one ventricle and not the other, it appears that lesions may occur in single muscle bundles and that some of the perplexing problems of the heart may be due to disturbances of the individual muscle bundles.

The concept that the two ventricles are different offers a working theory which may reconcile, in a manner better than has been possible heretofore, the functional activities with the structure and chemical constitution of the heart. As such its value remains to be proved or disproved.

It should be pointed out that at present the concept may be of practical application, although it does not answer the question as to whether these differences between the ventricles (or the muscle bundles) are

29. Masayama, T., and Riesser, O.: Ueber die Beziehungen des Glykogens zu Kreatin und Kreatinphosphorsäure im Kaninchenmuskel, Biochem. Ztschr. **234**: 323, 1931.

inherent, i. e., developmentally or originally qualitatively different or acquired after birth, owing to the greater amount of work done by the left ventricle (or single muscle bundles).

SUMMARY AND CONCLUSIONS

It has been established that the concentrations of creatine of the left and right ventricular muscles of the heart are different, the former having the greater concentration. Attention has also been called to correlations between creatine content and age and weight of the heart. From the standpoint of creatine-creatinine metabolism, it is significant that when the creatine content of voluntary muscle exceeds about 400 mg. (the probable saturation point) a corresponding elevation in the cardiac muscle also occurs, and further, that the retention of creatinine in renal disease has an augmenting influence on the creatine content of both cardiac and voluntary muscle.

In addition to embryologic, anatomic, physiologic and pathologic observations, chemical evidence is now presented pointing to the fact that the left and right ventricles are different muscles.

These differences justify the concept that the heart is not a uniform muscle but that it is made up of several qualitatively different muscles. The significance and possible practical value of this concept are discussed.

THORACIC STOMACH

REPORT OF FIVE CASES

HARRY W. GOODALL, M.D.
AND
LYMAN H. HOYT, M.D.
BOSTON

In September, 1931, in a patient who had been under observation for some years, there suddenly developed severe symptoms suggestive of obstruction high up in the gastro-intestinal tract. The patient was admitted to the New England Deaconess Hospital. A roentgenogram showed that two thirds of her stomach was in the thoracic cavity. The diagnosis of hernia of the stomach through the diaphragm, with obstruction at the pylorus, was made. The details will be given in the first case that we report. Treatment was without avail, and the patient died.

Fortunately a postmortem examination was permitted, and several unusual things were found. Two thirds of the stomach was in the thoracic cavity as the roentgenograms had indicated. Of greater importance, however, was the anatomic finding of an esophagus that was foreshortened by at least 4 cm and probably more. The significance of this short esophagus was overlooked at the time, and we all considered the diagnosis to be hernia of the stomach through the diaphragm.

This patient had complained for some considerable time of a peculiar type of dyspnea, to be described later, which we could never explain to our own satisfaction. On finding so large a part of the stomach in the thorax, the cause of dyspnea was evident. We recalled the cases of two other patients with the same type of dyspnea for which we had been unable to find any adequate reason. They were sent for and examined roentgenologically at the hospital with a special request that the length of the esophagus be determined. In these two cases the entire stomach was found to be in the thorax, and the esophagus in each case was found to be foreshortened. By this time it was evident that we were not dealing with hernia but with a congenital foreshortening of the esophagus which had prevented the descent of the stomach from the thorax, where it normally develops, into the abdominal cavity where it is normally found.

This was a clinical condition that was entirely unfamiliar to us. We could find no reference to it in the most recent textbooks, and we felt that we had recognized a condition that had escaped previous observation. However, in a review of the literature on "hernia of the dia-

phragm" we have been able to find seven similar cases reported. By far the most important case is the one reported by Bailey [1] in 1919. He found, during the regular dissection of the body of a man, 77 years of age, that the entire stomach was in the thoracic cavity and that the esophagus ended at the level of the third costal cartilage instead of extending to the normal level of the tenth thoracic vertebra.

So important are his findings that we repeat some of the pertinent facts:

> Upon opening the abdominal cavity we found only the pyloric antrum projecting through the esophageal opening of the diaphragm for a distance of 6 cm. Upon opening the thorax, the stomach, which was entirely in the thoracic cavity, was found lying between the pleural cavities, and behind the pericardium in the posterior mediastinum. The stomach was completely surrounded with a serous sac consisting of the normal peritoneal pockets of the stomach.

He recognized the fact that this was in no sense a hernia and that the stomach had developed in the thorax. He explained the existence of the sac by the fact that the peritoneal pockets of the stomach develop before the stomach and the diaphragm begin their descent. When the diaphragm descended, it left behind it the stomach, which was anchored by the esophagus, and from necessity elongated these peritoneal pockets which remained continuous with the peritoneal cavity. He gave the name of thoracic stomach to this condition.

So far as he could determine from his review of the literature, he was the first to recognize this condition. Our own review would seem to confirm this view although we are not sure but that the short esophagus was observed in some of the early reported cases of hernia of the diaphragm and that the significance was overlooked. Attention should also be called to an article by Brun, Masselot and Jaubert de Beaujeu [2] published in 1922 in which they reported finding by roentgen rays a case of "non-descent of the stomach with inversion, the movement of rotation around the vertical axis being towards the right instead of the left." Unfortunately they made no observations as to the length of the esophagus.

About five years after Bailey's report was published, LeWald [3] wrote an excellent article from the point of view of the roentgenologist, entitled "Thoracic Stomach: Differentiation from Eventration and Hernia of the Diaphragm." In this article he described two cases of thoracic stomach. Since then Roberts [4] has reported one case, Morris [5]

1. Bailey, P.: A Case of Thoracic Stomach, Anat. Rec. **17**:107, 1919.
2. Brun, Masselot and Jaubert de Beaujeu: J. de radiol. et d'électrol. **6**:278, 1922.
3. LeWald, L. T.: Thoracic Stomach: Differentiation from Eventration and Hernia of Diaphragm, Radiology **3**:91, 1924.
4. Roberts: Brit. J. Radiol. **32**:17, 1927.
5. Morris, H.: Case of Thoracic Stomach, Radiology **13**:265, 1929.

one case, Weitzen [6] one case and Lyons [7] one case. Lyons, however, missed the significance of the foreshortened esophagus as he made the diagnosis of "diaphragmatic hernia, thoracic stomach."

Without question Bailey [1] deserves the credit of calling attention to the fact that thoracic stomach is a definite clinical entity. We can find no instance in the literature in which the internist or the surgeon has recognized the condition. In reporting our five cases, the largest number yet reported in a single series, we believe that we are calling attention for the first time to the clinical significance of its recognition as a definite entity. In four of our five cases it was possible to make a probable clinical diagnosis of thoracic stomach before the roentgenologic diagnosis was made.

REPORT OF CASES

CASE 1.—A woman, aged 60, had been under our observation for some years for minor complaints. For two or three years she had a low grade secondary anemia which did not respond to treatment.

One year before her admission to the hospital she complained of dyspnea that had been developing and increasing for about a year. This dyspnea was of a panting type, like that seen in one who has been running. As she came into the office and sat down, we observed the dyspnea and asked her whether she had been running. She replied, "Wait a minute until I get my breath, and I will tell you about it." At the time the pulse rate was 94. Her breathing became normal in a few minutes, and she gave her history. The attack which we observed was brought on by the effort of walking from her car into the office. Any ordinary exertion about the house brought it on. It was more marked after eating, and she had learned from personal experience to eat small meals and to keep quiet for some time afterward.

Her previous history, so far as it pertained to this condition, was as follows: As far back as she could remember, she could not overeat and be comfortable. When she ate too heavy or too highly spiced foods or when she drank too much liquid with a meal she would feel so "stuffed" that she would regurgitate a part of the meal. Occasionally she would force herself to vomit, and this gave prompt relief. Nausea was not present as a rule but did occur at times. There was no gas, gastric distress or any other symptom of indigestion. As soon as she regurgitated or vomited she felt as well as ever. She had never considered that she had indigestion and had never consulted a physician for indigestion.

Physical examination at this time gave negative results. Her weight was 175 pounds (78.28 Kg.); her height, 5 feet and 8 inches (188.7 cm.). She had gained 10 pounds (4.53 Kg.) in the past year. The electrocardiogram showed a left ventricular preponderance but revealed no other abnormalities. Examination of the lungs gave negative results. The blood pressure was 165 systolic and 105 diastolic.

Three months before this examination she had been under observation at a well known sanatorium. Gastro-enteric roentgenograms were not made, but she was told that the flat plate of her chest showed an enlarged heart. We were unable

6. Weitzen, M.: Diaphragmatic Hernia with Severe Anemia, Am. J. Roentgenol. **28**:808, 1932.

7. Lyons, C. G.: Thoracic Stomach, Am. J. Roentgenol. **23**:67, 1930.

to demonstrate any enlargement by percussion. The apparent enlargement of the left border of the heart was evidently formed by the shadow of the thoracic stomach.

We reduced her weight 10 pounds without bringing about any relief of her symptoms. Soon after she began to complain of palpitation as well as of dyspnea. After completing this reduction we did not see her again until the onset of her last illness.

Ten days prior to her admission to the hospital on Sept. 11, 1931, she was seized with severe cramps in the upper part of the abdomen, associated with nausea and vomiting. She was at a summer resort at the time, and the local physician who was called made a diagnosis of food poisoning. Castor oil was

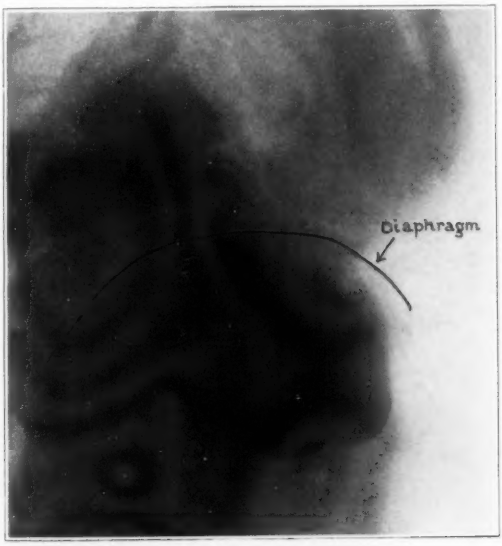

Fig. 1.—Lateral view of stomach of patient 1. Two thirds of the stomach is above the diaphragm. The patient was so ill that the length of the esophagus could not be demonstrated by roentgenograms, but at autopsy it was found to be foreshortened.

given, and the bowels moved freely, without relief from the pain in the epigastrium. The condition gradually but steadily became worse. For thirty-six hours before her admission to the hospital she had been unable to keep anything in her stomach; the pain in the epigastrium was extreme; there was frequent vomiting, and on the morning of her admission she vomited a little blood.

At the time of admission she was in a state of extreme exhaustion and was quite dehydrated. There were constant nausea and vomiting. The bowels had been moving, and gas was being passed without difficulty. There was no distention or tenderness of the abdomen, and no masses were found by palpation. The heart and lungs were normal. The temperature was 99 F., the pulse rate 90, and

the respiratory rate, 18 per minute. A diagnosis of obstruction high up in the digestive tract was made. Critical though her condition seemed, we thought it practical to attempt a careful roentgen examination. This was done, and two thirds of her stomach was found to be in the thoracic cavity. The diagnosis of hernia of the stomach through the diaphragm with obstruction at the pylorus was made. There had, however, been no history of fall, accident or undue strain.

A left phrenectomy and a jejunostomy were performed on Sept. 15, 1931, but this was not followed by any relief of the symptoms, and she died on the following day.

Fig. 2 (case 1).—Anteroposterior view. Two thirds of the stomach is above the diaphragm. The roentgenogram is shown as evidence that there is no indication of the obstructing duodenal ulcer, except that the barium did not pass through the pylorus.

At necropsy it was found that two thirds of the stomach was in the thoracic cavity. The esophagus was foreshortened by at least 4 cm., and probably more. There was a sharply demarcated ulcer, 1 cm. in diameter, situated on the posterior wall of the pylorus; this had caused the obstruction and brought about the patient's death. There was a sac present which consisted, as in Bailey's [1] case, of the normal peritoneal pockets of the stomach.

Four important points in connection with this examination should be noted: 1. None of us present at the necropsy recognized the sig-

nificance of the short esophagus at the time. We believed this to be a case of hernia of the stomach through the esophageal opening of the diaphragm. 2. Roentgen examination failed to give any suggestion of ulcer of the duodenum. 3. An ulcer of the duodenum was revealed that had never given any symptoms until it caused an obstruction. 4. The greater part of the stomach was found above the diaphragm, which explained the dyspnea and subsequent palpitation. Our interest, at the moment, was centered on this last fact, as we recalled the two other patients with a similar type of dyspnea in whom no satisfactory diagnosis could be made.

Both of these patients, as we have noted, were sent to the hospital with a request for a special examination for the determination of the length of the esophagus and the determination of the position of the stomach. Both proved to have thoracic stomach. The histories were as follows:

CASE 2.—The patient, a woman, was 68 years of age when the diagnosis was made. She first came under observation at the age of 56, complaining of dyspnea on slight exertion, of a year's duration; this was increasing in intensity until, at the time she was seen, she was short of breath on very slight exertion. When she sat down, it quickly passed away. At the time her weight was 177 pounds (80.28 Kg.) and her height, 5 feet and 1 inch (154.9 cm.). She had gained 10 pounds in the past year.

The history relating to the digestive function was as follows: As long as she could remember, she had had a sense of substernal fulness if she overate. When this occurred she would frequently regurgitate a little food, without nausea or any distress; occasionally she would vomit the entire meal and feel relieved. She stated that she never had indigestion.

As she came into the office she presented the same type of "panting" as that presented by the first patient, and she, too, said, "Wait a moment until I get my breath." Her pulse rate at the time was 80. In a few moments her breathing was normal, and she gave her history. A thorough physical examination failed to reveal any cause for the dyspnea except her possible obesity. Reduction in weight, however, failed to relieve her symptoms in any degree.

She was not seen again for five years, owing to a change in residence, and at this time she was 61 years of age. At this visit she complained of dyspnea which was more marked than before. Her history during this interval was as follows: Two years previously she had experienced for the first time substernal oppression if she overate; this was promptly relieved by vomiting. There was no nausea, gas or any other symptom of indigestion. Six months later, after a hearty meal she had a sudden attack of severe pain in the left side of the neck and the left shoulder, which extended down the left arm. The pain was "terrific" for ten or fifteen minutes; then she vomited the entire meal with an immediate relief of the acute symptoms, but it was several hours before she felt normal again. During the attack the breathing was labored, and there was marked palpitation. During the succeeding six months she had six or seven similar attacks, all as severe as the first, and they all occurred after "overloading her stomach." They were all relieved by vomiting. There had been no recurrence of the attacks during the past year, as she had learned not to overeat. Three physicians had seen her in these attacks; one diagnosed the condition acute indigestion, and the

other two, angina pectoris. Roentgenograms had been taken, but no satisfactory explanation was found. Physical examination at this time failed to show any satisfactory cause for her dyspnea.

On request she was examined roentgenologically again with the thought of a probable thoracic stomach. The roentgenogram showed the entire stomach above the diaphragm. The fluoroscope demonstrated the esophagus entering the stomach at the level of the ninth thoracic vertebra. The pylorus alone extended through the esophageal opening. The stomach appeared to be considerably dilated.

This case was complicated by a hernia of the colon, probably through the esophageal opening of the diaphragm, as was demonstrated by a barium sulphate enema. The colon extended to the left, nearly to the costophrenic angle, and then looped back to the midline, meeting the hepatic flexure at the esophageal opening.

Fig. 3 (case 2).—A large portion of the colon is in the pleural cavity.

CASE 3.—A woman, 68 years of age, was referred to us in 1920 for dyspnea of eight months' duration "due to obesity" and for the purpose of reducing her weight. She had gained 25 pounds (11.34 Kg.) in the previous three years. Her weight was 156 pounds (70.76 Kg.); her height, 5 feet and ½ inch (153.6 cm.).

As she came into the office she presented the same type of dyspnea seen in cases 1 and 2, and she was obliged to rest a few moments before she could give her history. Slight exertion made her short of breath. This was more marked after eating, and she had found that she felt much better when she sat down for an hour after eating. Her dyspnea was even more marked on lying down. If she did not have three pillows when she retired, her breathing would become difficult even though it was normal while she was sitting up.

Her digestive symptoms had never been pronounced. As a young woman she had attacks of "nervous indigestion" every spring and fall when she was overtired. These attacks consisted of regurgitating part of the meal or of vomiting the entire

meal when she overloaded her stomach. There was no nausea, gas or any other symptom of indigestion. She had been free from these attacks for years, as she had learned not to "overeat."

Careful examination failed to show any cause for her dyspnea other than obesity. Reduction in weight relieved her dyspnea when she was lying down, but otherwise there was no change. She has been seen at frequent times since, her dyspnea has gradually increased, and of late there has been some palpitation.

She was examined roentgenologically with the possibility of thoracic stomach in mind. The entire stomach was above the diaphragm, and the esophagus was seen by fluoroscope to enter the stomach at the level of the eighth thoracic vertebra.

Fig. 4.—This roentgenogram shows a typical thoracic stomach which up to the time of our investigation had been diagnosed as "hernia of the stomach through the esophageal opening of the diaphragm." The foreshortened esophagus is demonstrated beyond question, and in this case about two thirds of the stomach is above the diaphragm.

In these three cases the greater part of the stomach was above the diaphragm, and we shall from now on refer to such cases as cases of the first type. In the next two cases that we shall report the greater part of the stomach was below the diaphragm, and we shall refer to such cases as cases of the second type. This distinction is made as the clinical symptoms vary according as the bulk of the meal is above or below the diaphragm.

We were unfortunate in being unable to obtain a roentgenogram in any of our three cases showing the foreshortened esophagus. A roentgenogram from a typical case is shown which clearly reveals the fore-

shortened esophagus with about two thirds of the stomach above the diaphragm (fig. 4). This is a fairly recent case which was diagnosed by Morrison [8] as "hernia of the stomach through the esophageal opening, of the short esophageal type."

The next two cases that we report are cases of the second type. In both instances the diagnosis of thoracic stomach was suspected, and the patients were referred for special examination as to the length of the esophagus.

Fig. 5 (case 4).—This roentgenogram demonstrates the foreshortened esophagus that just fails to reach the esophageal opening of the diaphragm; a small portion of the fundus of the stomach is seen above the diaphragm.

CASE 4.—A woman was first seen in 1923 at the age of 48. Her weight was 155 pounds (70.30 Kg.); her height, 5 feet and 1½ inches (156.2 cm.). For nearly ten years she had complained of marked hyperacidity with gas and burning in the stomach, that had resisted all treatment. With frequent small meals and alkalis she was comfortable, but the moment she broke her diet or gave up taking

8. Morrison, L. B.: Diaphragmatic Hernia of Fundus of Stomach Through Esophageal Hiatus, J. A. M. A. **84**:161 (Jan. 17) 1925.

alkali the symptoms recurred. During this period a complete roentgen examination was made twice; the first time nothing abnormal was found, and the second time a duodenal ulcer of suspicious character was reported. The latter time the results of the physical examination were negative aside from the fact that she had a tenderness over the gallbladder. A fractional test meal showed a marked hyperacidity. There was no blood in the stomach contents or in the stools. Another complete gastro-enteric roentgen examination, including the gallbladder, was made in 1923 and was reported to give negative results. Previous clinical diagnoses had been made of ulcer of the stomach and the duodenum and of disease of the gallbladder. Operation had been advised but refused. We were unable to make a satisfactory diagnosis, but we put her on the regular treatment for ulcer, with relief of her symptoms. Whenever she overstepped her diet or gave up the alkalis the symptoms promptly returned. She complained of dyspnea, but only on exertion and we did not associate this with her digestive symptoms.

Reduction in weight to 135 pounds (61.13 Kg.) relieved her dyspnea but did not in any way alter her digestive symptoms. Soon after this a progressive chronic polyarthritis developed, and she was under the care of an orthopedic surgeon who gave her a diet for arthritis.

In October, 1932, she returned, saying that the diet she was following for her arthritis had greatly aggravated her digestive symptoms which she now described as "coals of fire in her stomach." The only thing that relieved her was soda, and she had taken "tons of it and was afraid to continue." During this interval she had been thoroughly examined roentgenologically, again with negative results. Dyspnea had not been a prominent symptom. At this time the results of a physical examination were negative aside from the fact that there was acute tenderness with a definite muscular rigidity over the gallbladder.

In view of the fact that her symptoms were so persistent and that repeated roentgen examinations had failed to demonstrate any abnormality of the gastroenteric tract, we suspected the possibility of thoracic stomach or hernia of the stomach through the diaphragm. We sent the patient to the New England Deaconess Hospital the following day with a special request for an examination of the esophagus, stomach and gallbladder. The gallbladder was normal. It was found that the esophagus fell just short of reaching the diaphragm and that a very small portion of the fundus of the stomach was in the thorax.

Case 5.—A woman was seen first in 1920 when she was 57 years of age. Her height was 5 feet and 1 inch; her weight, 139 pounds (63.04 Kg.). Six months before she weighed 150 pounds (68.04 Kg.). She had reduced her weight at the advice of her physician. Reduction in weight, however, did not relieve her symptoms.

For one year she had complained of symptoms of hyperacidity which, while slight at first, had gradually increased in severity up to the point where she was distressed all of the time. According to her past history she had never presented any digestive symptoms before this occurrence. In spite of treatment she had grown progressively worse. She complained of dyspnea on exertion; this was more marked after eating. However, it was not a disturbing symptom.

On physical examination she showed a moderate degree of thickening of the external arteries; the heart was slightly enlarged to the left; there was a mitral systolic murmur transmitted to the axilla; the second aortic sound was accentuated; the specific gravity of the urine was 1.010; there was the slightest possible trace of albumin, and casts were found in the urine. The blood pressure was 150 systolic and 100 diastolic. There was definite evidence of disease of the heart and kidneys.

There was definite tenderness over the gallbladder but no muscular rigidity. A fractional test meal showed a moderate hyperacidity. There was no blood in the stomach contents or in the stools. A complete gastro-enteric roentgen examination was made with the diagnosis of a "possible duodenal ulcer." With the usual treatment for ulcer the symptoms were relieved, but when she deviated from this regimen, the symptoms returned.

In 1921, after an indiscretion in diet, she had an attack of acute abdominal pain with tenderness in the region of the gallbladder. There was no temperature, nausea, vomiting or jaundice. Her local physician made a diagnosis of gallstones and advised operation. This attack lasted three days. She was not operated on.

After this she was more careful of her diet, and although she was always conscious of "indigestion" she was fairly comfortable.

In 1930, after another "hearty meal" she had a second attack, similar to the previous one. Since then she has been very careful not to overeat, and there has been no recurrence of these attacks.

Since this time dyspnea and palpitation have been the distressing symptoms. The blood pressure had gradually increased until at the time of this examination it was 200 systolic and 120 diastolic. Dyspnea and substernal pressure after eating, and numbness down the left arm, also after eating, were the predominating symptoms. She definitely associated these symptoms with overeating. Physical examination of the heart failed to show sufficient change to explain all the symptoms; she was sent to the hospital on Dec. 15, 1932, and the usual roentgen examination was requested. Roentgenograms showed an esophagus that just failed to reach the esophageal opening of the diaphragm, and a small portion of the fundus of the stomach was seen above the diaphragm. In certain aspects this case differs clinically from the other four cases, as the patient had definite cardiorenal disease.

FREQUENCY OF THORACIC STOMACH

Including our five cases only twelve cases have been reported in the literature. This seems to indicate that the condition is rare. We believe, however, that the condition is a common one which has been overlooked, as the presence of the stomach, or a part of the stomach, in the thoracic cavity has been considered to be hernia of the stomach through the esophageal opening of the diaphragm. We are referring, of course, to the congenital cases and not to the traumatic cases which belong in a class by themselves.

This is a matter of surprise as the literature on hernia of the diaphragm [9] is quite complete. As far back as medical records go, cases

9. Richards, L. G.: Nontraumatic Hernia of Diaphragm, Ann. Otol., Rhin. & Laryng. **32**:1145 (Dec.) 1923. Bowditch, H. I.: Treatise on Diaphragmatic Hernia, Buffalo, Jewett, Thomas & Co., 1853. Nothnagel, H.: Specielle Pathologie und Therapie, Vienna, A. Hölder, 1894, Supp. no. 1-6-G-178. Ritvo, M.: Hernia of Stomach Through Esophageal Orifice of Diaphragm, J. A. M. A. **94**:15 (Jan. 4) 1930. Truesdale, P. E.: Diaphragmatic Hernia: Its Clinical Aspect from Trauma in Children, J. A. M. A. **77**:993 (Sept. 24) 1921; New England J. Med. **207**:385, 1932.

have been reported. We can divide these reports into two distinct periods depending on the advent of roentgen examination.

Before the discovery of the roentgen ray the cases were found by the pathologist, the anatomist and rarely by the surgeon. It was considered a rare condition. The herniated portion was described as going through certain weak spots of the diaphragm resulting from developmental errors. If the foreshortened esophagus was discovered, its significance was overlooked.

With the improvement of roentgen technic, during routine gastroenteric examinations a portion of the stomach could be found above the diaphragm in persons in whom the condition was unsuspected. This has stimulated further investigations, and today all roentgenologists agree that hernia of the stomach is a common condition.

Morrison [8] and Healy [10] deserve the credit for demonstrating its frequency. They discovered this by accident. In 1922 they began a special study of the fundus of the stomach with the idea of determining some method whereby an early diagnosis of a malignant condition of the cardia could be made.

In order to get a clear picture of the fundus they "filled" the stomach with barium sulphate, put the patients in certain positions (supine, Trendelenburg, etc.) and then applied pressure over the epigastrium. During these special examinations they found that a portion of the fundus was "herniated" through the diaphragm in twelve cases. In 1925 Morrison [8] reported a total of forty-two cases of this type, and six months later Healy [10] brought the total up to fifty-three. These findings stimulated other roentgenologists to make similar examinations, with the result that many cases are now to be found in the literature.

Morrison [8] and Healy [10] classified these cases as hernia of the stomach through the esophageal opening of the diaphragm, and designated the cases in which a considerable portion of the stomach was in the thoracic cavity as "hernia of the short esophageal type."

From what we can find in the literature, this classification has been accepted by all of the roentgenologists with the exception of LeWald,[3] who recognized thoracic stomach.

We question the frequency of the occurrence of hernia through the esophageal opening. We admit its possibility, but we are certain that the roentgenologist has overlooked many cases of thoracic stomach and cases of true hernia of the diaphragm.

In order to support this contention it is necessary to review briefly the embryology of the organs concerned.

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10. Healy, T. B.: Symptoms Observed in 53 Cases of Non-Traumatic Diaphragmatic Hernia, Am. J. Roentgenol. **13**:266, 1925.

EMBRYOLOGY OF THE FOREGUT AND OF THE DIAPHRAGM

Unfortunately the embryology of the foregut and of the diaphragm have not been thoroughly worked out, but enough has been done to make the occurrence of the conditions described explainable.

The primitive gut starts as a straight tube which promptly becomes differentiated into a foregut, a midgut and a hindgut. From the foregut, which is relatively short, develop the esophagus and the stomach, the stomach appearing as a dilatation of the hind portion of the foregut. From the esophageal portion of the foregut the esophagus and the trachea develop. In front of this portion is the pharynx. This separation of the esophagus and the trachea begins in the early part of the third week of the embryo. The first indication is a longitudinal groove on the inner surface of its ventral wall. At this point the esophagus stops growing lengthwise, but begins to widen in order to form two tubes, the future trachea and the esophagus of the same caliber as the original esophagus. As this change takes place there is a temporary atresia of the esophagus in order to protect the lung, which is developing from this primitive trachea, from the possible inhalation of extraneous matters. By the beginning of the fourth week this longitudinal groove has deepened to complete separation, and two tubes are formed, connected only at the pharyngeal opening. The tube with the blind ending is the future trachea from which the lungs develop.

Once this separation is complete, under normal conditions, the atresia of the esophagus is relieved, and the esophagus resumes its growth. Three developmental errors may, however, occur at this point: 1. The atresia may not be relieved, giving rise to congenital atresia of the esophagus. 2. Widening of the esophagus may advance to an abnormal degree, giving rise to an abnormally wide esophagus. 3. The esophagus may fail to resume its growth, giving rise to thoracic stomach. In other cases growth of the esophagus is resumed, but, for some reason which we cannot explain, fails to reach its normal length. In some cases of thoracic stomach the esophagus appears to be abnormally wide, and it is suggested that this may be one reason for the occurrence of the anomaly, as increase in width would probably result in foreshortening.

We are obliged to consider the possibility that the diaphragm in its descent goes to an abnormally low position, leaving the esophagus behind. We can find no mention of such an occurrence, however.

Bailey,[1] in discussing the cause, thought that the anlage of the stomach was too far forward on the foregut. No other theories have been advanced.

True hernia of the diaphragm results from improper fusion of its various layers during its development, the most common fault being

found in an improper closure of the pleuroperitoneal canal. In true hernia the esophagus goes through the esophageal opening normally, and the herniating fundus passes up through one of these weak points.

These two definite conditions being presented, there remains a third possibility to be considered, namely, "hernia of the stomach through the esophageal opening of the diaphragm." Strictly speaking there is no esophageal opening of the diaphragm. As the diaphragm develops, two strong muscular bands, attached to the crura, develop. These two muscles closely surround the esophagus, leaving no opening. Any congenital error of these two muscles gives symptoms at birth, or soon after, and not late in life.

Morrison [8] and Healy [10] admitted this fact but claimed that with long-continued "indirect pressure," such as obesity, long-continued cough or other strains, a portion of the fundus is herniated and dilates these muscles, causing hernia.

It is evident that muscles of this character could not lose their elasticity unless the pressure was continuous; consequently such dilation does not seem probable. If, as we believe, these are cases of thoracic stomach, the esophageal opening would from necessity be larger than normal, owing to the fact that the portion of the stomach passing through the opening has a caliber larger than that of the esophagus, and the muscles in approximating the viscus would present a wider space. Furthermore it is difficult to understand the mechanics of "indirect pressure." No one would eat a meal comparable to the amount of barium sulphate that has to be given to demonstrate the hernia by roentgen examination.

In the two cases of the second type and in other cases which we have not reported it is demonstrated that, as the stomach begins to empty, enough barium sulphate remains in the herniated portion to show that it is still above the diaphragm and to make it appear to be fixed there. Morrison [8] stated that this type of hernia is easily overlooked during a routine gastro-enteric examination, on account of the fact that as soon as the stomach begins to empty there is a spontaneous reduction of the hernia. In both of the two cases, however, this was shown not to be the fact. In both, as the stomach began to empty, enough barium sulphate remained in the "herniated portion" to demonstrate without question that the herniated portion was fixed above the diaphragm and that reduction did not occur.

We believe that this herniated portion of the stomach is fixed in a position above the diaphragm by the foreshortened esophagus, and we can find no roentgen evidence to contradict this opinion. Roentgenologists, with the exception of LeWald,[3] have failed to recognize thoracic stomach and, in consequence, have paid little or no attention to the length of the esophagus.

If we are correct in our supposition, it is easy to understand why this herniated portion is so easily overlooked during the ordinary roentgen examination of the gastro-enteric tract and why such unusual methods as those described by Morrison [8] are required to fill the herniated portion.

Morrison [8] observed that "in nearly all hernia cases the esophagus seems a trifle enlarged." This supports our theory, already mentioned, that one reason why the esophagus fails to reach the diaphragm is that its caliber is abnormally enlarged.

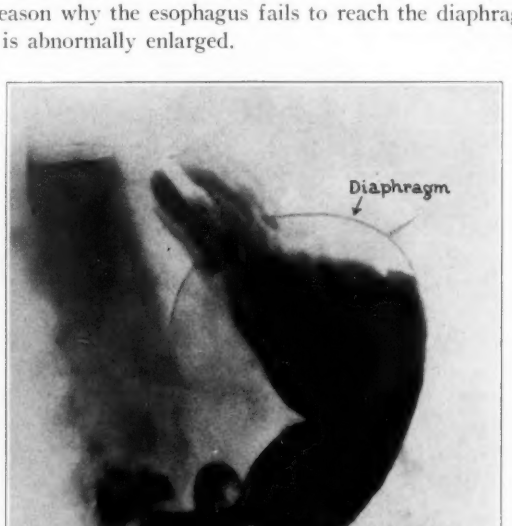

Fig. 6 (case 5).—The stomach is beginning to empty, yet enough barium sulphate remains in the small portion of the stomach above the diaphragm to demonstrate the fact that this is not a case of hernia through the esophageal opening. It is evident that the short esophagus is holding this small portion of the fundus above the diaphragm. From this roentgenogram it is evident that by fluoroscopic examination the mass of barium sulphate may appear to be reduced, but it is to be remembered that the fluoroscope shows the mass of barium alone and cannot demonstrate the position of the stomach itself. This figure suggests that any tension on the stomach is in the downward direction, yet the small portion of the stomach still remains above the diaphragm.

Some of Morrison's [8] observations require further comment. He stated that small hernias are difficult to demonstrate in a roentgenogram. With the fluoroscope, however, the small herniated portion can be seen passing up and down through the esophageal opening. Fluoroscopic

observations are limited largely to the activity of the mass of barium sulphate and we should expect that with a full stomach this fixed portion of the stomach would fill and empty with normal peristalsis. There is no evidence, however, that the stomach itself moves up and down through the opening.

We are unable at the present time to give definite statistics as to the frequency of thoracic stomach. It is interesting, however, to note that a diagnosis of hernia of the stomach through the esophageal opening of the diaphragm has been made at the New England Deaconess Hospital in forty-seven cases. The length of the esophagus was undetermined in twenty-two cases. In twenty-one cases a short esophagus was demonstrated, and in four cases the esophagus was seen to pass through the esophageal opening of the diaphragm. We conclude that twenty-one cases were cases of thoracic stomach, and four, cases of true hernia of the diaphragm. We realize that this is a comparatively small number of cases, but from a review of the literature on "hernia of the diaphragm" we believe that they are highly significant.

SYMPTOMS OF THORACIC STOMACH

Bailey's [1] patient lived to be 77 years of age without any symptoms referable to the condition. As the condition is congenital this is not a matter of surprise. We believe that many persons have lived their natural lifetimes without the condition being suspected.

When symptoms occur, they are the result of two distinct mechanisms: (1) interference with normal peristalsis of the gastro-intestinal tract and (2) embarrassment of the thoracic organs.

Symptoms may occur at birth, in which event there must be some other congenital disturbance, the most probable one being some interference with the normal rotation of the stomach. It is even possible that the different types of stomach described in "hernia" are the result of abnormal disturbances in the rotation of the stomach as a result of the short esophagus.

Furthermore, it is probable that with developmental errors of the esophagus other developmental errors of the digestive tract occur. Attention has already been called to the occurrence of the abnormally wide esophagus. In the forty-seven cases observed at the New England Deaconess Hospital, two showed a diverticulum of the esophagus; one, a diverticulum of the duodenum, and five, a diverticulosis of the colon. In one case there was an eventration of the diaphragm. In one doubtful case reported as one of "hernia" there was a congenital atresia of the duodenum.

In many of these cases giving rise to symptoms early in life the symptoms do not occur until the child changes from a milk diet to a general one.

If symptoms do not occur during the first five years of life they do not, as a rule, occur until early or late adult life. Just what occurs to interfere with normal peristalsis at this time is not quite clear. In many instances it is certain that complications occur, especially duodenal ulcer, which appears to be not infrequent in thoracic stomach. In others it is possible that the lack of muscular tone is responsible.

In the cases of the first type it would appear that symptoms, as a rule, do not appear until late in life, when the lung loses its elasticity or the myocardium begins to degenerate. The symptoms may be divided into two distinct groups: 1. Cardiorespiratory: These symptoms predominate in the first type of case, in which the bulk of the stomach is above the diaphragm. 2. Gastro-intestinal: These symptoms predominate in the second type of case, in which the bulk of the stomach is below the diaphragm.

Dyspnea.—Dyspnea is a characteristic symptom in the first type of case. With ordinary activity, such as walking a short distance or doing the easiest kind of work, such as dusting, the patients begin to "pant" as if they had been running. If they sit down for a few minutes, the breathing becomes normal again. During this period, they do not even feel like talking. If the heart is normal, there is no particular increase in pulse rate. This dyspnea is more marked immediately after eating. When the stomach is empty, activity may not give rise to dyspnea. If the patient lies down immediately after eating, the dyspnea is often more pronounced. If there is evidence of myocarditis, an increased pulse rate may be observed.

In the second type of case dyspnea is not a symptom unless there is some definite interference with the action of the diaphragm. In true hernia of the diaphragm dyspnea is a frequent symptom, and in cases of thoracic stomach of the second type with ulcer, dyspnea may be a symptom.

Morrison [8] reported that in some of his patients who were operated on, the margins of the esophageal opening were thickened, and the stomach wall showed more or less dense cicatricial-like thickening over the portion that had become herniated, which indicated some inflammatory process. The roentgenologist demonstrated ulcer in some of these cases, but in our first case reported the occurrence of the ulcer was entirely overlooked in the roentgenogram. One can only conclude that the roentgenologist is definitely limited in his ability to make a positive diagnosis in the cases showing abnormally developed stomachs.

Cardiac Symptoms.—In the first type of case a sense of substernal fulness is common if the person overeats. LeWald's patient said "she could feel her stomach in her chest" after overeating. In all of the

patients who have complained of this sensation immediate relief has been obtained by regurgitation or vomiting. In only one of the twelve cases reported were there symptoms suggestive of angina.

Angina Pectoris.—Symptoms of angina pectoris are by no means uncommon in cases of true hernia of the diaphragm. In thoracic stomach, however, these symptoms never occur except in the event of complications. In one of our cases a diagnosis of angina and acute indigestion had been made, but in this case the colon had herniated through the esophageal opening. It is probable that in cases of ulcer in the region of the esophageal opening with adhesions symptoms of angina may occur. It is probable that any symptom of angina may suggest the herniation of some other abdominal organ.

Palpitation.—In the first type of case palpitation occurs only when myocardial changes are present or when an ulcer at the esophageal opening interferes with normal peristalsis. In true hernia palpitation is frequently a distressing symptom. When it occurs in thoracic stomach we must assume that the stomach has become adherent to the muscles of the esophageal opening, as a result of ulcer.

Gastro-Intestinal Symptoms.—From the standpoint of the patient gastro-intestinal symptoms are practically negligible in the first type of case; yet, clinically, they are suggestive. They are essentially mechanical, and occur only when the patient overeats.

The usual story is that with the ingestion of too much food, too rich foods or too highly spiced foods or the ingestion of too much liquid with the meal there is a sensation of fulness, and a part of the meal, occasionally the entire meal, is regurgitated. This occurs without nausea, gas or any other symptom of indigestion, and this regurgitation immediately relieves the sensation of pressure. When real symptoms of indigestion occur in this type of case, it suggests that some complication, such as ulcer, is present.

In the second type of case regurgitation is rare, but may occur. In one case, in which the small portion of the fundus was demonstrated as being fixed above the diaphragm, the patient complained of a sensation of fulness after a few mouthfuls of food, evidently after the intake of enough food to fill this "herniated" portion. Occasionally regurgitation would occur, but as a rule if the patient waited a few minutes, she could finish the meal without discomfort. Evidently the pressure of this small amount of food dilated the constricting opening and permitted the food to pass through without further discomfort.

The real digestive symptoms in this type of case are those of a persistent, often severe hyperacidity.

In the majority of the cases which have been overlooked during the roentgen examination the diagnosis has been disease of the gallbladder,

ulcer of the duodenum, ulcer of the stomach or appendicitis. Many of the patients have been operated on with negative results. One unfortunate woman was operated on three times—once for appendicitis, once for gallstones and once for adhesions—before the "hernia" was demonstrated. In several cases gallstones have been demonstrated and operations have been performed without relief of symptoms, and later examination has shown the presence of "hernia."

Acidity.—In our two cases a fractional test meal showed a marked hyperacidity. In both cases the stomach contents and the stools were negative for blood. In both of these cases, as in cases of ulcer, there were periods of remission, but at no time were the patients free from symptoms.

One suggestive feature of the acidity, which may be characteristic, is the fact that if a hearty meal is eaten, the acidity is almost immediate; if a small meal is taken, the acidity does not appear until from one to four hours after eating.

Abdominal Pain.—Abdominal pain has been observed only in cases of the second type and in these only during the attacks of severe gastric distress. Pain, tenderness and muscular rigidity in the epigastrium and in the region of the gallbladder have been observed during these severe attacks.

Dysphagia.—Dysphagia is a frequent and distressing symptom in true hernia of the diaphragm. It is not a symptom of thoracic stomach. It is not reported to be a common symptom of "hernia through the esophageal opening of the esophagus" as we should expect it to be.

Nausea and Vomiting.—Nausea and vomiting may occur during the acute attacks of hyperacidity in the second type of case, but, as a rule, the occurrence of these symptoms would suggest some complication, such as duodenal ulcer.

Gas.—The presence of gas is unusual in the first but common in the second type of cases. There is nothing characteristic about it, however. In true hernia of the diaphragm gas is often a distressing symptom, and its occurrence aids in the clinical differentiation of thoracic stomach and true hernia.

Constipation.—Constipation is frequently referred to in reported cases of hernia of the diaphragm, but, so far as we can determine, it has no particular bearing on the condition, unless the intestines are herniated and are to be found in the thorax.

Other Symptoms.—We have attempted to confine our observations to the relatively few cases which we are certain are cases of thoracic

stomach. In the literature of diaphragmatic hernia, however, many distressing symptoms are reported which have led to the diagnoses of asthma, pulmonary tuberculosis, myocarditis, angina pectoris and practically all of the abdominal diseases.

From the observations that we have already made it is possible to understand why such diagnoses would be made. There remains, however, one observation which should be commented on, namely, the occurrence of anemia in "hernia" of the diphragm.

In the most recent report calling attention to this finding, Weitzen [6] entitled his article "Diaphragmatic Hernia with Severe Anaemia." Our first case presented a moderate anemia that did not respond to treatment. At postmortem examination we found that the patient had an ulcer of the duodenum that was overlooked in roentgen examination and that was probably responsible for her anemia. Morrison [8] reported cases in which the patients vomited blood but failed to show any ulcer. We believe that the roentgenologist has definite limitations in this field of diagnosis in cases of "hernia of the diaphragm." It is our opinion that anemia is no more frequent in cases of "hernia" than in the ordinary course of life, and that its occurrence suggests ulcer.

TREATMENT

It can be definitely stated that thoracic stomach is a problem that belongs to the field of the internist and not to that of the surgeon, for, because of the short esophagus, the abnormality cannot be corrected. Medical treatment, from necessity, has its limitations, but it can at least prevent unnecessary operations and unnecessary medication such as treatment with digitalis. It can do much more than this, since it is possible to keep the patient in comparative comfort and perhaps to prevent complications. In order to do this it is necessary to have the complete cooperation of the patient just as in all incurable conditions, such as diabetes and tuberculosis.

The diagnosis must be definitely made and the condition fully explained to the patient.

For the most part the treatment is dietary. The first essential is to avoid overeating. Frequent small meals must be taken. Rich foods and highly spiced foods must be avoided. Fluids with meals should be restricted. A bland diet such as that recommended by Alvarez should be prescribed. Meat should be eaten once a day at least. The clothing about the thorax and abdomen should be loose. It is desirable to maintain the patient at his normal weight. The upright position should be maintained for at least one hour after the principal meals of the day.

Patients presenting the symptoms of hyperacidity should be treated as if they had ulcer of the stomach or duodenum, regardless of whether the roentgen findings are positive or negative as to the occurrence of ulcer.

If, under these conditions, the patient cannot be made comfortable, or if distressing symptoms occur, some complication should be suspected.

CONCLUSIONS

Thoracic stomach is a definite clinical entity belonging in the field of the internist. We believe the condition to be a fairly common one. Its seeming rarity is due to the fact that cases, especially of the second type, have been overlooked by the roentgenologist and probably by the pathologist.

We believe that the clinical symptoms are characteristic enough to permit a tentative diagnosis.

Dyspnea of the type described, occurring in the latter part of life, suggests thoracic stomach.

Unmitigated gastro-intestinal symptoms with negative routine roentgen findings should make one suspicious of thoracic stomach.

One must, of course, depend on the roentgenologist for the final diagnosis, and this necessitates a routine determination of the length of the esophagus in all gastro-enteric examinations.

The occurrence of ulcer in thoracic stomach cannot always be demonstrated by roentgenograms.

We hope that this report will stimulate the anatomist and the pathologist to make more careful observations of the organs involved, giving special attention to cases of the second type.

We are at the present time engaged in a complete review of "hernia of the diaphragm" and a more detailed report will be made later.

51 Bay State Road.

CHRONIC IDIOPATHIC STEATORRHEA

ROENTGENOLOGIC OBSERVATIONS

ALBERT M. SNELL, M.D.
AND
JOHN D. CAMP, M.D.
ROCHESTER, MINN.

The first hint of a clinical syndrome in which diarrhea was associated with metabolic disorders appeared in Trousseau's [1] celebrated lecture on tetany. It is now well recognized that certain types of fatty diarrhea may be associated with serious depletion of calcium and tetany. These clinical syndromes are described under the names of "nontropical sprue," "idiopathic steatorrhea," "Gee's disease," "Gee-Herter disease," "adult celiac disease," "intestinal lipodystrophia" and various other names. If one may judge from current reports in the literature and from our experience, this condition is probably considerably more common than is generally believed.

The literature on this disorder has been completely reviewed in recent reports by Linder and Harris,[2] Bauer and Marble,[3] Bennett, Hunter and Vaughan,[4] physicians of the Mayo Clinic, and numerous other authors. The clinical picture, as established by previous reports, is that of fatty diarrhea with associated changes in the metabolism of calcium and phosphorus, the extent of these last mentioned phenomena depending on the duration and the severity of the diarrhea. The condition closely simulates tropical sprue, differing from it chiefly in the fact that its victims have resided in temperate climates. It usually pursues a chronic course with exacerbations and remissions, and in certain cases it appears to represent a long-standing deficiency in the

From the Division of Medicine and the Section of Roentgenology, the Mayo Clinic.

1. Trousseau, Armand: Lectures on Clinical Medicine, London, The New Sydenham Society, 1868.

2. Linder, G. C., and Harris, C. F.: Calcium and Phosphorus Metabolism in Chronic Diarrhoea with Tetany, Quart. J. Med. **23**:195 (Jan.) 1929.

3. Bauer, Walter, and Marble, Alexander: Studies on the Mode of Action of Irradiated Ergosterol: II. Its Effect on the Calcium and Phosphorus Metabolism of Individuals with Calcium Deficiency Diseases, J. Clin. Investigation **11**: 21 (Jan.) 1932.

4. Bennett, T. I.; Hunter, D., and Vaughan, J. M.: Idiopathic Steatorrhea (Gee's Disease); Nutritional Disturbance Associated with Tetany, Osteomalacia and Anaemia, Quart. J. Med. **1**:609 (Oct.) 1932.

digestion and absorption of fat and other substances which began in early life and continued into maturity; for this reason it has been referred to as adult celiac disease. It appears to be somewhat more common among females, but cases of marked severity have been reported as affecting persons of both sexes. The principal complaint is usually that of long-continued diarrhea, which may be intermittent or continuous. In most instances, two or more bulky, foul, grayish stools are passed daily. Exacerbations of the diarrhea are not uncommon, and in some of our cases appear to have been more common in the spring. Each episode of diarrhea may be associated with increasing loss of weight, flatulent indigestion and attacks of active tetany. Loss of weight is usually extreme, and with it there is a corresponding degree of malaise and physical debility. The appetite is often capricious, and there may be marked anorexia. There is often a history of latent tetany of long standing, with muscular cramps and paresthesia, and in certain instances this is the most conspicuous feature of the disease, antedating the diarrhea by considerable periods. A history of glossitis is common. Pains in the bones and joints are not infrequent, especially in the more advanced cases, and may represent the earliest symptoms of depletion of the skeletal reserve of calcium.

On physical examination the patients are usually markedly emaciated and dehydrated. Some are of constitutionally substandard types, and in at least three of our cases there were evidences of serious growth defects which obviously dated back to early life. Marked pallor is commonly noted. Often there is active glossitis, as well as areas of atrophy on the tongue. Hypothermia, lowered blood pressure and a slow pulse are not uncommon. The abdomen is usually distended and is in sharp contrast to the general emaciation, a feature which numerous writers have noted. Kyphosis, pelvic contractures and other signs of osteomalacia may be apparent. The deep reflexes may be absent, but there are rarely sufficient neurologic findings to suggest the diagnosis of subacute combined degeneration of the spinal cord. Peripheral neuritis and eruptions resembling pellagra have been described. In two of our cases, definite edema of the nutritional type was encountered, and this feature has also been noted by other observers.

Laboratory data are of definite diagnostic value, and the abnormalities of metabolism of calcium and phosphorus may be regarded as sufficient to distinguish this disorder from other conditions associated with tetany, as has been shown by Aub and his associates,[5] and by

5. Aub, J. C.; Albright, Fuller; Bauer, Walter, and Rosemeisl, Elsie: Studies of Calcium and Phosphorus Metabolism: IV. In Hypoparathyroidism and Chronic Steatorrhea with Tetany with Special Consideration of the Therapeutic Effect of Thyroid, J. Clin. Investigation **11**:211 (Jan.) 1932.

Bauer and Marble. The concentration of calcium and of phosphorus in the blood are both reduced; the urinary excretion of calcium is also low, but the fecal excretion of this substance is increased. There is also marked increase in the urinary excretion of phosphorus. The reduced value for serum phosphorus serves of itself to distinguish this condition from true parathyroid tetany, in which the reverse is the rule. Marked secondary anemia is usually present, or blood smears may reveal well developed macrocytosis. In some of our cases, however, small and irregular red blood cells predominated in the smears. Complete achylia is not particularly common, but lowered gastric acidity has been reported by numerous observers. The basal metabolic rate may be considerably reduced, although in many cases the muscular hypertonicity associated with latent tetany may interfere with obtaining a true basal reading. In the stools there is excess of neutral fat and fatty acids, and experiments in metabolism have shown that the loss of fat from this source may be considerable. The values for serum protein are often reduced to a level at which any excess of intake of fluid will result in the development of edema.

Roentgenologic observations reported in the literature concerning this condition have been limited to the gastro-intestinal tract and the skeletal system. Osteoporosis and osteomalacia have been noted frequently. Dilatation and redundancy of the colon have been commonly observed, but abnormalities of the stomach or small intestine have not been noted except in the case described by Radl and Fallon.[6] These authors noted marked narrowing of the second and third parts of the duodenum, suggesting ulceration with periduodenal adhesions. An ulcer was also observed in the first portion of the duodenum, producing gastric retention for which gastro-enterostomy was performed. It was suggested that the narrowing of the duodenum had interfered with the normal passage of pancreatic secretion.

The cases reported in this paper were observed at the Mayo Clinic. Significant data on all cases are given in the accompanying table. Clinical features of the first five cases have been reported previously and will not be repeated here. However, special attention is given to roentgenologic observations in all cases in which information was available. Similar roentgenologic findings have not been reported heretofore.

In all of the seven cases (except case 2) roentgenologic studies of the gastro-intestinal tract were made. In cases 1 and 3 the results were negative. In the remaining four cases roentgenologic examination revealed definite abnormalities in the contour and motility of the small intestine.

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6. Radl, R. B., and Fallon, Madelein: Nontropical Sprue with Duodenal Involvement and Tetany, Arch. Int. Med. **50**:595 (Oct.) 1932.

Summary of Cases

Case	Age, Yrs.	Sex	Diarrhea: Duration	Diarrhea: Severity, Grade	Tetany: Duration, Years	Tetany: Severity, Grade	Glossitis	Amenorrhea	Approximate Loss of Weight, Lbs.	Hemoglobin, per Cent	Erythrocytes, Millions	Gastric Acidity, Free and Total*	Serum Calcium, Mg. per 100 Cc. Range†	Plasma Phosphates, Mg. per 100 Cc. Range‡	Basal Metabolic Rate, per Cent	Osteoporosis	Comment
1	32	F	Lifelong	2	7	2	+	+	45	54	3.60 macrocytes	40/56	6.3 11.3	4.4 6.6	+12	None	Under observation 8 years; in good health at time of writing; normal pregnancy 2 years before time of writing; taking calcium lactate and cod liver oil
2	33	F	Intermittent, 6 to 7 years	1	5	2	0	+	40	54	4.09	18/38	6.3 8.2	2.3 4.5	+ 8	Marked	Somewhat relieved by high vitamin intake and calcium; died 3 years after treatment began from intercurrent infection
3	51	F	6 to 7 years	Intermittent, 2 to 4	2	3	0	Postmenopause	20	62	3.91	0/10	4.9 7.7	2.4 4.6	Not determined	None	Tetany controlled by parathyroid extract-Collip but diarrhea intractable; patient left hospital against advice
4	47	F	20 years	2	20	2	+	+	25	38	3.71	0/10	6.3 11.6	4.0 4.1	+17	None	Tetany controlled by parathyroid extract-Collip and high vitamin diet; finally "cured" by viosterol; gained 23 pounds (10.4 Kg.); well 2 years after treatment began
5	47	M	1 year	3	10	1	+	..	50	75	4.89	44/56	6.8 8.6	2.9 3.9	—15	None	Relieved by viosterol and calcium lactate and high protein diet; had definite nutritional edema at onset; well several months after treatment began
6	44	M	6 months	3	0	0	+	..	26	70	3.42	8/28	8.0 10.5	2.2 3.4	— 4	Slight	Much benefited originally by viosterol and high protein diet; easily upset by dietary error
7	45	F	8 months	3	0	0	+	+	22	67	3.82	46/58	7.8 9.0	2.8 3.0	— 6	None	Benefited by viosterol but very low tolerance for fat; one severe episode of diarrhea in month before time of writing

* In terms of cubic centimeters of tenth-normal sodium hydroxide required to produce end-point in 100 cc. of strained gastric content.
† Method of Kramer and Tisdall.
‡ Method of Fiske and Subarrow.

REPORT OF CASES

CASES 1, 2 and 3.—Case 1 has been reported by Snell and Habein;[7] case 2, by Constam and Partch,[8] and case 3, by Snell.[9]

CASE 4.—The clinical features of this case have been reported by Snell.

Roentgenologic examination on Feb. 7, 1930, revealed the deformity of an ulcer in the first portion of the duodenum. There was some dilatation of the second portion of the duodenum and some smoothing out of the usual serrated outline; the jejunum did not appear to be abnormal. Gastro-enterostomy afforded relief from the duodenal ulcer, but subsequently tetany and nutritional edema developed. Examination on August 8 revealed an increase in the degree of

Fig. 1 (case 4, Aug. 8, 1930).—Roentgenogram showing smoothing out of the usual contours of the duodenum and jejunum.

smoothing out of the duodenal contour and a smooth outline of the jejunum, with a marked increase in the prominence of the usual outlines of the valvulae conniventes, suggesting edema of the mucosa (fig. 1). The gastro-enteric stoma was functioning well. Examination on June 9, 1931, revealed a marked increase in the degree of the changes observed on the previous examination. The normal markings of the valvulae conniventes were completely absent, and the barium sulphate appeared to "clump up" in smooth masses (fig. 2). There was also some

7. Snell, A. M., and Habein, H. C.: Tetany and Chronic Diarrhea, Am. Int. Med. **1**:694 (March) 1928.

8. Constam, C. R., and Partch, W. T.: An Unusual Case of Nutritional Disturbance, Showing Symptoms of Pellagra, Osteomalacia, and Tetany, Minnesota Med. **12**:40 (Jan.) 1929.

9. Snell, A. M.: Chronic Steatorrhea with Tetany: Report of Two Cases, M. Clin. North America **15**:1593 (May) 1932.

Fig. 2 (case 4, June 9, 1931).—Roentgenogram showing an increase in the degree and extent of changes in the jejunum since the previous examination. There are dilatation of the jejunum and absence of the usual markings of the valvulae conniventes.

Fig. 3 (case 4, Dec. 1, 1931).—Roentgenogram showing the change in the appearance of the jejunum coincident with clinical improvement. The smoothing out of the jejunal contour is less marked even than in figure 4 and suggests a return toward normal.

dilatation of the small intestine. At this time the colon began to assume a smooth contour, with absence of haustrations. Definite clinical improvement followed this period of observation, and on Dec. 1, 1931, examination revealed regression of the changes observed at the previous visit (fig. 3). The jejunum now compared in appearance with that seen on Aug. 8, 1930. The smoothing out of the contour of the small intestine was less marked, and the outlines of the valvulae conniventes were again discernible. It is significant that the progression of roentgenologic changes was in keeping with the severity of the symptoms, and that definite restoration toward normal marked the clinical improvement of the patient.

CASE 5.—Clinical features of this case have been reported by Curry [10] and Snell.[11]

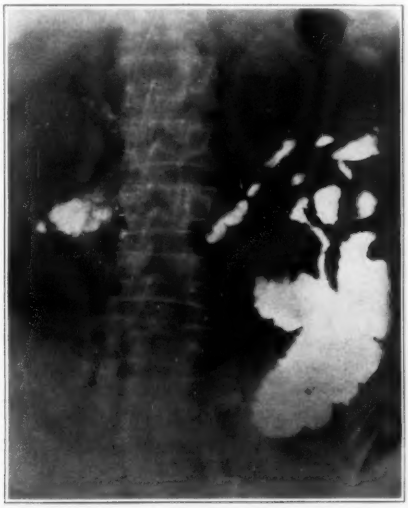

Fig. 4 (case 5, Oct. 18, 1932).—Roentgenogram showing the elongated, smoothly outlined masses of barium in the proximal part of the jejunum. There is an absence of the markings of valvulae conniventes in the involved region.

Roentgenologic examination on Aug. 16, 1932, revealed a normal stomach and duodenum. Special study of the small bowel was not made at this time. Therefore, it is possible that alterations in its contour were overlooked. On October 18, the stomach and duodenum appeared to be normal. There was delay in the passage of barium sulphate through the jejunum, and its outline was abnormally smooth (fig. 4). In many places the opaque meal seemed to "clump" in elongated masses similar to those observed in case 4. In many places the barium adhered to the

10. Curry, F. S.: Chronic Steatorrhea with Tetany: Report of a Case, Proc. Staff Meet., Mayo Clin. **7**:501 (Aug. 31) 1932.

11. Snell, A. M.: Discussion, Proc. Staff Meet., Mayo Clin. **7**:502 (Aug. 31) 1932.

walls of the jejunum after the bulk of the meal had passed, giving it a peculiar, flecked appearance.

Case 6.—A man, aged 44, complained chiefly of diarrhea, anemia and loss of weight. There was no history of tetany, but roentgenograms of the pelvic bones gave questionable evidence of osteoporosis. The concentration of calcium and phosphorus in the blood was reduced, and there was roentgenographic evidence of disease of the duodenum and jejunum, a matter which will be considered later. This patient was also benefited by the administration of viosterol and calcium lactate and the dietary restriction of fat. Through a period of six months his condition slowly improved, and he gained 6 pounds (2.7 Kg.). Recently an

Fig. 5 (case 6, Oct. 10, 1932).—Roentgenogram of the stomach and jejunum, revealing the smooth contour of the proximal part of the jejunum. Prominent mucosal markings are seen in the duodenum, and there is a tendency of the barium to clump in smooth, elongated masses in the proximal part of the jejunum.

exacerbation of the diarrhea occurred, which may be attributed to dietary indiscretion.

Roentgenologic examination on Feb. 3, 1932, revealed a normal stomach. There was dilatation of the second and third portions of the duodenum, with delay in the third portion suggesting an extrinsic lesion, possibly pancreatic in origin. The motility of the small bowel was observed fluoroscopically, but abnormalities were not noted. A special investigation of the mucosa of the small intestine was not made. An attempt was made to examine the colon by means of an enema of barium sulphate, but the colon was dilated and contained much fluid and barium from previous studies, and an adequate examination was impossible. On October 10, the stomach was reexamined, and a special study of the small bowel was carried out. The stomach was normal, except that its contours were shaggy, suggesting

hypertrophy of the mucosa. The dilatation previously noted in the duodenum was still present, and the contour was somewhat irregular. The jejunum also had a shaggy contour except for areas here and there where the barium clumped in smooth, elongated masses (fig. 5). The caliber of the jejunum appeared to change at different intervals during the examination, and smooth and apparently narrowed regions later were dilated, suggesting the presence of spasm. Motility was delayed.

CASE 7.—A woman, aged 45, had suffered from severe diarrhea, weakness and loss of weight for eight months. Her case is similar to that of the patient in case 6. The difficulty was of short duration, and signs of tetany were absent. The values for blood calcium and phosphorus were reduced, and there was definite secondary anemia. Immediate benefit followed the administration of the same therapeutic procedures as those applied in case 6, but there have since been numerous rather severe relapses, controlled by rigid dietary restriction of fat. At the present time the woman is slowly improving.

Roentgenologic examination of the colon on Feb. 17, 1933, revealed that the lumen was somewhat narrowed and smooth, particularly in the distal portion. There was some smoothing of the outline of the terminal part of the ileum. The stomach and first portion of the duodenum were normal. Barium in the colon prevented study of the small bowel, and the patient did not remain for a second examination.

COMMENT

The general causes of tetany in digestive disorders have recently been reviewed by Marble and Bauer [12] and may be listed as follows: (1) dietary deficiency of either calcium or phosphorus; (2) dietary excess of calcium over phosphorus, or vice versa; (3) deficiency of vitamin D (which may be primary or due to a loss of fat-soluble vitamins in the stools [Linder and Harris]); (4) long-standing diarrhea, especially if large amounts of fat are lost; (5) any condition hindering absorption from the upper part of the gastro-intestinal tract, and (6) biliary or intestinal fistulas of long standing.

The clinical syndrome and metabolic disturbances in chronic steatorrhea with tetany have been ascribed primarily to disturbance in the absorption of fat from the intestine, which in turn prevents proper assimilation of calcium and phosphorus from ingested food. The tetany and decalcification, in other words, represent a calcium-phosphorus deficiency due to faulty absorption. According to Telfer,[13] the availability of calcium for absorption is dependent on the presence of free hydrochloric acid in the gastric content, which affects the solubility of certain compounds of calcium in the diet. When the alkaline bile and pancreatic juice mix with the content of the upper part of the intestine, calcium is

12. Marble, Alexander, and Bauer, Walter: Calcium and Phosphorus Metabolism in a Case of Nontropical Sprue with Associated Tetany, Arch. Int. Med. **48**: 515 (Sept.) 1931.

13. Telfer, S. V.: Studies in Calcium and Phosphorus Metabolism: III. The Absorption of Calcium and Phosphorus and Their Fixation in the Skeleton, Quart. J. Med. **17**:245 (April) 1924.

precipitated as calcium phosphate. Telfer inferred that absorption of calcium must therefore occur in a relatively small area of the duodenum and upper part of the jejunum. The significance of this observation will be apparent when the known anatomic lesions of idiopathic steatorrhea are considered.

In the condition under consideration, as has been stated, there are deficient digestion and absorption of fat, which may be attributed to some pancreatic disorder, or to some intrinsic lesion of the duodenum or jejunum; the few available observations made at necropsy in these cases tend to substantiate this view. In Whipple's [14] cases there were extensive deposits of neutral fat and fatty acids in the intestinal mucosa and in the mesenteric and retroperitoneal lymph nodes. Chronic passive congestion and cloudy swelling of the viscera were also noted. In Salvesen's [15] case at necropsy were found atrophy of the pancreas and spleen, as well as parenchymatous degeneration of the liver. In the first case reported by Blumgart [16] there were extensive deposits of fat in the intestinal mucosa and in the adjacent lymph nodes; atrophy of the liver and spleen and chylous ascites were also found. In his second case, the changes were somewhat similar. In his third case, discrete ulcers of the ileum and distention of the cecum with atrophy of its mucosa were noted, and deposits of fat in the intestinal mucosa were also observed; these were described as being composed of fat-laden phagocytic cells of unknown origin. In the case reported by Starr and Gardner,[17] atrophy, dilatation and passive congestion of the whole intestinal tract were noted. The mesenteric nodes were hyperplastic, and there were marked atrophic changes in the spleen and pancreas. Hemosiderosis of the liver and spleen were also observed.

On the basis of these anatomic observations, it would appear that in certain cases at least it should be possible to demonstrate roentgenologically evidence of disease in the upper part of the intestinal tract, and such changes have been noted in three of our seven cases. Furthermore, it was apparent in case 4 that the changes became less marked as the patient improved. It is felt that evidence of disease of the upper

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14. Whipple, G. H.: A Hitherto Undescribed Disease Characterized Anatomically by Deposits of Fat and Fatty Acids in the Intestinal and Mesenteric Lymphatic Tissues, Bull. Johns Hopkins Hosp. **18**:382 (Sept.) 1907.

15. Salvesen, H. A.: Observations on Human Tetany: 1. Spontaneous Tetany in Adults, Acta med. Scandinav. **73**:511, 1930.

16. Blumgart, H. L.: Three Fatal Adult Cases of Malabsorption of Fat: With Emaciation and Anemia, and in Two Acidosis and Tetany, Arch. Int. Med. **32**:113 (July) 1923.

17. Starr, Paul, and Gardner, Lois: A Biochemical Study of Two Patients with a Condition Simulating Sprue, Am. J. Trop. Med. **10**:283 (July) 1930.

part of the intestinal tract may be of diagnostic value in certain cases of this type.

It is evident from the roentgenologic findings that delayed motility and alterations in the mucosal relief of the small intestine, especially the jejunum, consisting of smoothing of the contours of the lumen, obliteration of the usual markings of the valvulae conniventes and clumping of the barium in elongated masses, occurred in all of our cases in which adequate roentgenologic examination was possible during the active stage of the disease. The roentgenologic findings suggested an inflammatory condition, with edema of the mucosa and infiltration of the walls, involving especially the small intestine and occasionally the stomach, duodenum and colon. The regression of the changes coincident with improvement in the clinical symptoms and inflammatory changes described at necropsy in similar cases would seem to substantiate this opinion. It is not held that these roentgenologic observations are characteristic only of chronic idiopathic steatorrhea, since they may occur in varying degrees in any diffuse inflammatory condition of the intestinal tract. Their presence, however, constitutes tangible evidence, during life, of alterations in the gastro-intestinal tract which have been suspected clinically and found at necropsy in this disease.

The similarity of this condition to sprue has been commented on, but references to roentgenologic studies of the gastro-intestinal tract in that disease are confined to one article by Pillai and Murthi,[18] who investigated nine cases. They found, in the acute forms, no indication of loss of tonus or motility, or other change in the stomach or intestines. In the subacute state there was slight loss of tonus and vigor of peristalsis of the stomach, with consequent delay in passage of content there. The same was true of the cecum and colon. The small intestine emptied rapidly, and spots of barium retained in the upper part of the cecum were interpreted as evidence of ulceration. In the chronic state changes were similar but more marked. There was no evidence of local ulceration of the small bowel. The cecum and transverse colon were dilated, and in one case the transverse colon contained a "pool" of barium. Diverticula observed in the colon were explained by atrophy of the mucosa and fibrotic changes in the muscle which affected the circular fibers before the longitudinal fibers. Pillai and Murthi stated, further, that when there are ulcerations in the mouth and upper part of the alimentary tract, there are no signs of ulceration lower down, and vice versa. From this it is concluded that there are two forms of the disease, the "ascending" and the "descending."

18. Pillai, M. J. S., and Murthi, K. N.: Radiological Signs in Cases of Sprue: A Study of Nine Cases, Indian J. Med. **12**:116 (June) 1931; abstr., Trop. Dis. Bull. **29**:8 (Jan.) 1932.

Roentgenograms of the skeletal system were made in three of the seven cases with which this paper is primarily concerned.

The bones seemed normal in one case; in the second, there was osteoporosis, and in the third, marked osteomalacia, with deformities of the pelvis and long bones, and pseudofractures (*Umbauzonen*). The skeletal changes in the last case were so comparable with the roentgenologic changes described by Looeser [19] in cases of hunger-osteomalacia that vitamin deficiency, which may be primary or secondary, is strongly suggested as a cause of the condition.

From the anatomic, physiologic and roentgenologic evidence presented, it is apparent that the clinical syndrome of idiopathic steatorrhea with tetany may be produced by inflammatory or atrophic lesions of the upper intestinal segments. As has been mentioned, the element of defective absorption of fat, mineral salts and vitamins may well be secondary to such lesions. Not all examples of this syndrome present definite intestinal lesions, however, and there is hardly sufficient evidence to justify the belief that the condition constitutes a clinical entity. The same clinical phenomena have been encountered in tropical sprue (Fairley [20]), which, as recent studies seem to indicate,[21] may be a deficiency disease approximating in some respects primary anemia. In a recent personal communication, Bauer [22] mentioned, among other possible causes of the syndrome, the question of deficient external pancreatic secretion. Holst's [23] recent report of a case of pancreatic carcinoma illustrates this point. Bauer also mentioned the possibility of this syndrome resulting from any disease which would produce a local lesion in the upper part of the intestinal tract, or any disease which would cause sufficient changes in the lymphatic structures of the intestinal tract to interfere with absorption of fat. The mechanical short-circuiting of the small intestine which occurs with gastrocolic or jejunocolic fistula will also produce steatorrhea and defective absorption of calcium, as Fairley and Kilner [24] have shown. These possibilities must be considered in any case in which the clinical syndrome under consideration

19. Looeser, E.: Ueber Spatrachitis und Osteomalacie: Klinische, röntgenologische und pathologisch-anatomische Untersuchungen, Deutsche Ztschr. f. Chir. **152**:210, 1920.

20. Fairley, N. H.: Sprue: Its Applied Pathology, Biochemistry, and Treatment, Tr. Roy. Soc. Trop. Med. & Hyg. **24**:131 (Aug.) 1930.

21. Castle, W. B., and Rhoads, C. P.: The Aetiology and Treatment of Sprue in Porto Rico, Lancet **1**:1198 (June 4) 1932.

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is presented, and the etiologic basis for defective absorption of fat and calcium must be sought for in each case.

In the different cases of our series, the previously mentioned etiologic factors varied considerably in significance. In case 4 there was possibly an actual temporary deficiency in diet or in vitamins. The patient often had periods of marked anorexia, and at these times diarrhea and tetany were particularly likely to develop. The principal therapeutic problem in this case was that of providing an adequate intake of food and an ample supply of vitamins. In cases 5 and 6, in which the difficulty was of relatively short duration, the presence of active jejunitis of unknown origin appears to have been of paramount importance. Whether such lesions are primary, or only, as is possibly the case in tropical sprue, a secondary manifestation of deficiency of some unknown substance or substances, cannot be definitely stated. In cases 1 and 2 there was much to suggest a life-long defect in the absorptive power of the upper part of the intestine and in the metabolism of calcium and fat. This statement applies in case 5 in which mild symptoms of tetany had been present for years before diarrhea finally became troublesome. In two of these three cases there was definite evidence of defective growth or of skeletal defects, suggesting persistence into adult life of some inherent abnormality of absorption of fat and calcium.

TREATMENT

Recognition of the fact that there is, fairly commonly, an inflammatory or degenerative lesion of the upper part of the intestine, in idiopathic steatorrhea, should serve, in our opinion, to modify the therapeutic approach. Treatment should meet the requirements laid down by Fairley for the treatment of tropical sprue: (1) rest of the alimentary tract, (2) restoration of the blood to normal and (3) supplying demonstrable deficiencies such as lowered concentration of calcium and of phosphorus in the blood and defective gastric secretion of hydrochloric acid. In our clinical experience with the cases mentioned in this review, it has been apparent that little can be accomplished for these patients unless rest of the alimentary tract and control of the diarrhea have been attained. Dietary regulation becomes, therefore, an essential of successful treatment. In some cases, restriction of the intake of fat and a high intake of protein may control the symptoms. The tolerance to fat appears to be variable. Some of our patients tolerated up to 100 Gm. of fat daily, but others were unable to utilize half this amount. In case 7, the tolerance was low; diarrhea developed if more than 40 or 50 Gm. of fat was given. The tolerance of these patients to fat can best be determined by a stay in the hospital where the excretion and intake of fat can be determined and the two compared. Exact measure-

ments of the amount of fat excreted are not often necessary; the appearance of the stool is characteristic if much fat is being excreted. Carbohydrate tolerance is also variable, as it is in the celiac disease of infants, and has to be determined by trial and error. So-called sprue diets furnish a convenient starting point for dietary adjustment. Proteins are usually tolerated without any particular difficulty, and diets high in protein have been used with particular success in treatment of the acute phases of the disorder. As the condition of the patient improves, fats and carbohydrates may be added.

The use of vitamin D, in the form of viosterol, appears to be of great therapeutic value. This fact is borne out by the experience of numerous workers. Bauer and Marble, after the administration of viosterol, noted prompt increase in absorption of calcium and phosphorus, elevation of the values for serum calcium and serum phosphorus, establishment of a positive calcium and phosphorus balance and marked improvement in clinical symptoms. Their observations may be taken as further evidence of the relationship of the syndrome just described to infantile tetany and rickets. Viosterol alone may suffice to keep the diarrhea and the depletion of calcium under control, but as a rule dietary regulation is also necessary.

Parathyroid extract-Collip is obviously only a symptomatic remedy in these cases, since it does not increase the utilization of calcium but causes increased liberation of this substance from the skeleton. In the presence of severe fatty diarrhea, its characteristic effect on the value for blood calcium is often obtained only with large doses. It appears to have little effect on the symptoms of diarrhea in many cases, although in Holmes and Starr's [25] cases it exerted a generally beneficial effect. As a means of controlling tetany it is highly effective, but its use should be continued only when necessary, the patient's bodily store of calcium meanwhile being fortified by large doses of calcium lactate given by mouth.

The anemia associated with this condition may often be a problem in itself. In a number of cases it has been of sufficient severity to simulate primary anemia, and in fact is distinguished from the latter condition chiefly by the presence of free hydrochloric acid in the gastric content and the absence of changes in the spinal cord. In the treatment of this sprue type of anemia, liver extract has been used with good effect, and Porter and Rucker [26] have described two cases in which the diarrhea was also greatly relieved by its use. Our own experience with

25. Holmes, W. H., and Starr, Paul: A Nutritional Disturbance in Adults Resembling Coeliac Disease and Sprue, J. A. M. A. **92**:975 (March 23) 1929.

26. Porter, W. B., and Rucker, J. E.: The Treatment of Nontropical Sprue with Liver Extract, Am. J. M. Sc. **179**:310 (March) 1930.

liver therapy has been limited, one patient (case 5) having apparently been originally made worse by its use; later he used liver extract with excellent effect. Marmite, a substance derived from yeast, has also been described by Vaughan and Hunter [27] as having a specific effect on the anemia of this disease.

CONCLUSION

In general, it may be said that if the diarrhea is kept under control, neither the depletion of calcium nor the changes in the blood will reach serious proportions. The treatment in these cases is, as we have already emphasized, a highly individualized problem, and one which calls for considerable resource on the part of the physician. It is well to remind the patient in advance that immediate good results do not necessarily mean freedom from relapses in the future. The best therapeutic responses have been obtained with cooperative patients who were willing to submit readily to changes in diet and medication, and to tolerate a certain amount of discomfort from these sources.

The prognosis appears to be fairly good. If the bones show extensive demineralization, the outlook is obviously not so favorable, although it is not necessarily hopeless. In cases in which the factors of dietary or vitamin deficiency predominate, much can be expected from treatment. In cases in which there are extensive pancreatic or intestinal lesions, there is reason to believe that greater difficulties will be encountered. The case reported by Radl and Fallon is in point. The whole matter of treatment may be summarized by the statement that it is wise to evaluate the most important etiologic factors in the individual case and then to direct treatment accordingly. Early diagnosis is imperative and should cause no difficulty, if the condition is considered when diarrhea is an outstanding factor. An excess of fat in the stools and reduction in values for blood calcium and blood phosphorus should assist in establishing the diagnosis. The roentgenologic appearance of the small bowel, although probably not specific for this disorder, may be of confirmatory value.

27. Vaughan, Janet M., and Hunter, Donald: The Treatment by Marmite of Megalocytic Hyperchromic Anaemia, Lancet **1**:829 (April 16) 1932.

News and Comment

COMING MEETINGS

American Medical Association, Cleveland, June 11-15, 1934.

American Society for Clinical Investigation, Hotel Chalfonte-Haddon Hall, Atlantic City, N. J., April 30.

Association of American Physicians, Atlantic City, N. J., May 1 and 2.

Book Reviews

Metabolic Diseases and Their Treatment. By Erich Grafe. Translated by Margaret Galt Boise, under the supervision of Eugene F. DuBois, M.D., and Henry B. Richardson, M.D. Price, $6.50. Pp. 551. Philadelphia: Lea & Febiger, 1933.

Nothing except in praise can be said of this excellent translation of Professor Grafe's treatise. The author is well known in this country as a student of metabolic problems, and a systematic exposition of his views will be welcome to all physicians. The book is one of those rare ones in which a really profound and scholarly discussion of the fundamentals of a subject by one conversant with them at first hand is combined with sound clinical knowledge. There are general sections on metabolism and on the chemistry of foods, followed by a discussion of the nature and treatment of nutritional disorders. Special sections follow on obesity, undernutrition and diabetes, to the last of which some 200 pages are devoted. Gout and other "inborn" errors of metabolism are dealt with next, and finally come sections on diabetes insipidus, calcareous diathesis and the formation of stones. The general plan with each subject is to analyze the underlying pathologic physiology and on this superstructure to erect the clinical discussion. The entire material is thoroughly documented with a full representation of American as well as foreign literature. Specialists will, of course, always disagree on minor points, but in this book all sides of the question are fairly presented, even though the author emphasizes his own views. The only point which I am inclined to criticize is the consideration given to a large number of German proprietary pharmaceuticals which, aside from their euphonious names, probably have little virtue.

Congrès français de médecine, Twelfth Session, 1932. Report 1: The Anatomic and Clinical Character of Malignant Granuloma.

This is an exhaustive study and review of all possible types of Hodgkin's disease, in an effort to place it definitely as a borderline inflammatory state, different from a purely neoplastic state, of the reticulo-endothelium. Confusion arises in the histologic picture, because the lesions show in a haphazard way all the polymorphic evolutionary and progressive changes that the mesenchymal tissue is capable of undergoing (inflammatory, fibrous and neoplastic) and follow stimulation by the virus. Even the cells of Sternberg are thought to be otherwise normal megakaryocytes. Stress is laid on the presence of eosinophils, the possible absence of the cells of Sternberg and, particularly, the presence of pruritus.

High voltage penetrating roentgen therapy produces the only remission of any duration. Suspected areas should be treated, but no prophylactic doses should be given. Superficial lesions should receive from 750 to 1,200 roentgen units, divided into daily doses, for from ten to fifteen days. Deep-seated lesions should receive from 4,000 to 5,000 roentgen units, from 1,000 to 1,200 units through each field. The treatment should last for from four to five weeks. The tension is set at from 180 to 200 kilovolts and the intensity at from 2 to 4 milliamperes, with filtration through from 0.5 to 1 mm. of copper and 1 mm. of aluminum.

Biologic and bacteriologic experiments have not proved any factor to be etiologic. Tuberculosis seems to have more than a casual relation, but no definite connection can be established.

The Modern Treatment of Syphilis. By Joseph Earle Moore. Price, $5. Pp. 535. Springfield, Ill.: Charles C. Thomas, Publisher.

From time to time books appear which stand out as landmarks in a subject so far as they rid themselves of the deadwood of tradition and by a consideration of actual facts formulate definitely a new point of view. Such a result, in our opinion, has been achieved by Moore in his discussion of the modern treatment of syphilis. Above all, he has stated clearly and on a rational basis the imperative reasons for prolonged, intensive and continuous treatment in early syphilis, in contrast with the widely different indications for therapy in the late stages, when the patient has built up his own immunity. Each phase of the subject is gone into in detail, and the conclusions are based on actual statistical material from the author's clinic or from the literature, and not on vague general impressions. One of the most attractive features of the book is that it is a personal one. Dr. Moore tells the story as he sees it, in a terse, dramatic style. Once started, it is hard to put the volume down as the thread of the argument unrolls. Here and there one may differ on fine points; this to the reviewer is a healthy sign; the author who completely protects himself against challenge produces at best a dreary compendium.

Space forbids a detailed discussion of the extensive material which Dr. Moore has handled; suffice it to say that there are chapters dealing with the biology of syphilis, with the various antisyphilitic drugs and special procedures, with the details of treatment of all forms and phases of syphilis, with the serologic problems and finally with the social aspects of the disease. The illustrations and charts supplement admirably the discussion in the text, and each chapter is followed by a well selected bibliography.

Arritmias. By Antonio Battro. Pp. 246, with 141 illustrations. Buenos Aires: Sebastian de Amorrortu, 1933.

This paper-bound volume presents an excellent discussion of the cardiac arrhythmias. It devotes several pages to the anatomy of the heart and then proceeds with a description of the methods of registering graphically the cardiac irregularities. One criticism might be interpolated: Much more space is devoted to the study of the cardiac rhythm by means of polygraphs and polygraphic tracings than in this country. That seems like a waste of time. The latter half of the book deals with the various types of arrhythmias from the point of view of the accompanying physiologic disorders, the clinical expression of the mechanistic disturbances and their polygraphic and electrocardiographic expressions.

The make-up and format of the book are excellent; the paper is of a high grade glossy quality on which the numerous figures are excellently reproduced. The book may be highly recommended to physicians who can read Spanish.

Principles of Human Physiology. By E. H. Starling. Edited and Revised by C. Lovatt Evans. Sixth edition. Pp. 1,122. Philadelphia: Lea & Febiger, 1933.

Professor Evans' recent revision of Starling's Physiology maintains, we believe, in every respect the high standards of the University College group. The tendency naturally is to stress the principles of general physiology, but the wider philosophy of the subject is so admirably blended with the special aspects of human physiology that whether the reader be biologist or medical student his needs are adequately served. Recent points of view receive thorough discussion, and the entire book bears evidence of critique and authoritative analysis. The format is attractive; the illustrations are good, and the references—mostly dealing with comprehensive articles—are carefully selected.

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